American Heart Journal

VOL. 29 MARCH, 1945 No. 3

Original Communications

THE POTENTIAL VARIATIONS OF THE THORAX AND THE ESOPHAGUS IN ANOMALOUS ATRIOVENTRICULAR EXCITATION (WOLFF-PARKINSON-WHITE SYNDROME)

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INTRODUCTION

IN 1930, Wolff, Parkinson, and White[1] reported a group of cases characterized by the following features: (1) the occurrence of paroxysms of tachycardia, heterotopic in origin; (2) complete absence of physical signs of heart disease when the heart rate was normal; (3) electrocardiographic peculiarities, of which the most striking were abnormal shortening of the P-R interval and a pronounced increase in the duration of the QRS complex; (4) reversion of the anomalous electrocardiogram to the normal form either spontaneously, after exertion, or after the administration of atropine. Isolated cases which seem to have been of a similar kind had previously been reported by Wilson,[2] Wedd,[3] and Hamburger.[4] In 1940, Hunter, Papp, and Parkinson[5] were able to find ninety cases of this type in the literature and to add to these nineteen cases which they had collected. This condition has been called the Wolff-Parkinson-White syndrome, but in order to avoid awkward forms of expression we shall more often refer to it as anomalous atrioventricular excitation.

A number of different hypotheses have been advanced to account for the peculiarities of cardiac mechanism which make this disorder unique. These hypotheses have recently been reviewed and classified by Hunter and his associates, and it is fair to say that none of them satisfactorily

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Presented in part before the Sixteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 5, 1943.

Received for publication May 9, 1944.

explains the syndrome in its entirety. The most promising and most widely accepted view was put forward independently by Holzmann and Scherf[6] and by Wolferth and Wood.[7] They suggested that the short P-R interval and the broad QRS complex are due to the transmission of impulses from auricles to ventricles by way of an accessory atrioventricular bundle, a strand of muscle of the sort described originally by Kent.[8] Quite recently, this conception has been supported by two important studies. In experiments on animals, Butterworth and Poindexter[9] passed action currents picked up from the auricular surface through a vacuum-tube amplifier and utilized the output to excite the ventricles. In this way they were able to obtain electrocardiograms strikingly similar to those seen in human cases of anomalous atrioventricular excitation. By reversing the connections and applying amplified ventricular action currents to the auricles they were also able to induce paroxysms of tachycardia simulating those often observed in this syndrome. Wood, Wolferth, and Geckeler[10] have reported a careful histologic search for muscular bridges between the auricular and the ventricular myocardium in a case of anomalous atrioventricular excitation in which death occurred during an attack of paroxysmal tachycardia. Three connections of this kind were found on the right side of the heart.

These studies are of very great importance, but they must be regarded as suggestive rather than decisive. The experiments of Butterworth and Poindexter[9] demonstrated that excitation of the epicardial surface of the ventricles by the action currents of adjacent auricular muscle, or inferentially by the transmission of auricular impulses across an accessory atrioventricular bundle, could account for the brevity of the P-R and the abnormal length of the QRS interval, and also suggested a way in which a physiologic or anatomic anomaly of this sort might lead to paroxysms of tachycardia. Nevertheless, they left many questions relating to these phenomena unanswered. Muscular bridges of the kind found by Wood and his co-workers[10] were originally described by Kent,[8] and have recently been observed by Glomset and Glomset[11] in hearts that were presumably normal. It would appear, therefore, that human hearts in which they can be found are much more numerous than those that exhibit anomalous atrioventricular excitation. This consideration raises doubt as to their significance.

In view of this situation, it seemed desirable to ascertain whether unipolar precordial and esophageal leads, which have proved of great value in the study of other abnormalities of the ventricular complex, would yield data consistent with the hypothesis in question.

CLINICAL OBSERVATIONS

We have had the opportunity of studying ten cases of anomalous atrioventricular excitation which were discovered in the course of routine electrocardiographic examination or referred to us for investigation.

Brief abstracts of the case histories are presented below. The electrocardiographic data will be considered separately.

CASE 1.—A schoolboy, aged 13 years and of somewhat deficient intelligence, entered the hospital Oct. 7, 1942, for the correction of convergent strabismus which had been present since infancy. Along the left margin of the sternum there was a moderately loud, rough, systolic murmur, but the heart was not enlarged; the blood pressure was normal, and there were no cardiac symptoms. A corrective operation on the eyes was performed October 29, and the patient's convalescence was uneventful.

CASE 2.—A male professor, aged 36 years, came in for a checkup examination on Feb. 14, 1942. He had no complaints referable to the heart and appeared to be in good health. Soft systolic murmurs were heard at the cardiac base and apex, but there was no enlargement of the heart either on physical or roentgenologic examination. Apart from the anomalous electrocardiogram, no abnormalities of any sort were discovered. Late in July, 1942, this man was found dead in his automobile, which was standing at the side of the road. He was known to have been normally active a few days prior to his death. The results of an autopsy carried out by the coroner could not be ascertained.

CASE 3.—A male storekeeper, 34 years of age, entered the hospital March 20, 1942, complaining of occipital headaches for the preceding four years, and of mild dyspnea on exertion and slight edema of the ankles for several months. During the preceding three years he had been subject to paroxysms of tachycardia, forty-five minutes to four hours in duration. The blood pressure was 186/116; there was slight edema of the ankles, and the heart was slightly enlarged to the left. The urine contained albumin and granular casts, and renal function was depressed (urea clearance, 29 and 22 per cent of normal). There was no improvement on a conservative regime, and a bilateral splanchnicectomy was performed Aug. 31, 1942. Twelve days later the patient was discharged; at this time the blood pressure was 105/55. He returned for a checkup examination on Aug. 16, 1943, and reported that he had had a few attacks of tachycardia, but was working regularly. The blood pressure was then 162/120; apart from the absence of edema, the physical signs were not notably different from those found on previous occasions. There was, however, a change in the electrocardiogram; the T deflections, previously inverted in precordial leads V_4, V_5, and V_6, had become upright. It has been observed that the inverted T waves often seen in hypertensive heart disease frequently return to normal after operations of the kind performed on this patient.

CASE 4.—A foundry worker, 30 years old, entered the hospital Nov. 11, 1942, complaining of attacks of nocturnal dyspnea and palpitation. Three attacks of this sort had occurred during the preceding three months. The duration of the paroxysms varied from ten to fourteen hours, and attempts to prevent them by the administration of digitalis and quinidine had not been successful. There was a moderately loud, apical, systolic murmur, but the heart was not enlarged either on physical or roentgenographic examination, and the blood pressure was normal. The rest of the physical examination and the routine laboratory tests were negative. The administration of quinidine, 0.2 Gm. three times daily, was advised, but this treatment failed to prevent occasional paroxysms of tachycardia.

CASE 5.—A young man, aged 34 years, was referred to the William J. Seymour Hospital (Eloise, Mich.) on July 30, 1941, for examination in connection with the Selective Service program. He presented no cardiac symptoms. The blood pressure was 190/120, and there were mild changes in the retinal arteries of the kind often associated with arterial hypertension. The heart was not definitely enlarged either on physical or roentgenographic examination. The remainder of the physical examination was negative.

CASE 6.—A male physician, aged 28 years, who was attached to the Heart Station, was found to have an anomalous tracing when he was used as a subject in the course of a test of some electrocardiographic equipment. He was subject to renal glycosuria, but was otherwise well, and physical and roentgenographic examination of the heart was negative.

CASE 7.—A male laborer, 37 years old, entered the hospital June 9, 1934, complaining primarily of joint pains associated with swelling and limitation of motion. For about three years he had also been subject to paroxysms of tachycardia lasting from twelve to twenty-four hours. These were accompanied by mild dyspnea, slight precordial distress, and occasional choking sensations. The heart was not enlarged, but roentgenographic examination disclosed slight widening and tortuosity of the thoracic aorta and minor prominence of the pulmonary artery. Frequent extrasystoles were noted, but no murmurs were heard, and the blood pressure was normal. The knees, elbows, and wrists showed changes characteristic of chronic atrophic arthritis, and there was some hypertrophic arthritis of the spine. The patient was under treatment for a considerable period, during which a number of paroxysms of tachycardia, supraventricular in origin, were observed. These were successfully treated with acetyl-β-methylcholine chloride and with quinidine. The regular administration of the latter reduced the frequency of the attacks.

CASE 8.—A female clerk, aged 24 years, requested an examination on July 29, 1943. She had been rejected for service with the Armed Forces on account of a cardiac murmur and arrhythmia. Examination disclosed a fairly loud, late systolic, apical murmur and an inconstant systolic click. Sinus arrhythmia and occasional extrasystoles were noted. The blood pressure was normal, and the remainder of the physical examination was negative.

CASE 9.—A male office worker, 25 years old, was examined Oct. 6, 1941, with reference to frequent attacks of rapid heart action during the preceding ten years. One of the most recent of these had persisted for thirty hours. Physical examination of the heart was negative, and the blood pressure was normal. Roentgenographic examination of the chest and the routine laboratory tests gave no further information.

CASE 10.—A housewife, aged 48 years, was admitted to the William J. Seymour Hospital (Eloise, Mich.) because of an involutionary psychosis early in February, 1941. She gave a history of paroxysms of tachycardia, but had no other symptoms referable to the heart. No cardiac abnormalities were discovered on examination, and the blood pressure was normal. This patient is still under observation; her mental condition has gradually deteriorated.

In summarizing the clinical aspects of these ten cases of anomalous atrioventricular excitation we may mention that all of the patients were under 50 years of age, and that all except two were males. Three ex-

hibited anomalies other than that involving the heart; we refer to the presence of renal glycosuria in Case 6, of mental deficiency and strabismus in Case 1, and of an involutional psychosis in Case 10. Half of the patients were subject to paroxysms of rapid heart action. Clinical evidence of structural heart disease was found in only one instance, in which it was associated with arterial hypertension. One other patient had an abnormally high blood pressure (Case 5), one had chronic atrophic arthritis (Case 7), and a third died suddenly and unexpectedly from an unknown cause (Case 2).

ELECTROCARDIOGRAPHIC OBSERVATIONS

Material.—The standard limb leads and unipolar* precordial leads from the six standard precordial points (Leads V_1 to V_6, inclusive) were taken in all ten of the cases upon which this report is based. Unipolar leads from the tip of the ensiform process (V_E) were taken in eight cases, multiple unipolar leads from the back and right side of the chest in five, and multiple unipolar leads from the esophagus in four. The esophageal leads were taken in the manner described by Nyboer,[12] and the unipolar limb leads according to Goldberger's technique.[13]

The analysis of our records would have been easier if we had taken all of the leads mentioned in every instance. Sometimes we did not do this because the time and length of the patient's visit did not offer the opportunity. More often, however, a number of these leads were not taken because the problems which prompted us to employ them at a later stage of our work had not yet presented themselves.

The Working Hypothesis and Its Implications.—We accepted, as a working hypothesis, the view that in cases of the kind under consideration auricular impulses reach the ventricles by way of an accessory atrioventricular bundle. If this is the case, it is clear that the order of ventricular activation during the first part of the QRS interval must depend to a considerable extent upon whether the ventricular muscle in which this bundle terminates lies on the inner or on the outer aspect of the ventricular wall. It must also be acknowledged that, if the existence of one anomalous tract of this kind is admitted, we cannot dismiss the possibility that two or more may exist. There are, moreover, reasons for supposing that, even if other atrioventricular bridges are present, the His bundle continues to function.

These considerations make the interpretation of the ventricular deflections which depict anomalous atrioventricular excitation particularly difficult. The situation is much more complicated than those encountered in the analysis of the curves that represent bundle branch block, ventricular hypertrophy, and myocardial infarction. In these conditions the cardiac impulse reaches the ventricles by way of the His

*The term *unipolar* is used to indicate that the exploring electrode was paired with a *central terminal* connected through resistors of 5,000 ohms to each of the extremity electrodes employed in taking standard limb leads. For practical purposes it may be assumed that the potential of a central terminal of this sort is not affected by the heart beat; or what amounts to the same thing, that it is zero throughout the cardiac cycle.

bundle and spreads through the ventricular walls from within outwards. The various types of QRS complexes inscribed in unipolar precordial leads under these circumstances may be interpreted with confidence because the principles involved have been established by recording and comparing the potential variations of the epicardial surface, the ventricular cavities, and the precordium in experiments on animals. We cannot, however, assume that a QRS pattern which has a known significance when ventricular excitation takes place in the normal fashion must have the same significance when auricular impulses are transmitted to the ventricles along anomalous paths.

Previous observers have found that when anomalous and normal beats are recorded in the same tracing, the sum of the P-R and the QRS interval is the same, or very nearly the same, for both. This suggests that the broad QRS complexes represent premature anomalous activation of the ventricular muscle, combined with normal activation by way of the His bundle. Assuming that this is true, we must conclude that, in relation to auricular events, some fraction of this muscle is activated earlier, but none can be activated later, than would be the case if the cardiac impulse reached the ventricles by way of the His bundle only. We may, then, refer to that part of the anomalous QRS complex which encroaches upon the normal P-R interval as the premature component. The point at which this component ends cannot be ascertained with certainty unless normal ventricular complexes have been recorded on the same tracing. In other cases we may consider that this point falls about 0.08 to 0.10 second ahead of the RS-T junction. We may also speak of the anomalous QRS complex as consisting of an anomalous component and a normal component. The former, which represents action currents produced by muscle activated by way of an aberrant pathway, is in part premature and in part superimposed upon the latter, which represents the action currents of muscle activated by the normal route. It has been observed that the premature component, that is to say, the premature part of the anomalous component, is almost invariably of relatively low voltage and displays no steep slopes. In the majority of cases it is fused with the first part of the succeeding fraction of the QRS complex, and gives rise to basal slurring or notching of the earliest prominent QRS deflection. The size and character of this premature component have been interpreted as evidence that when the aberrant impulse first reaches the ventricular muscle it spreads slowly and does not immediately gain access to the Purkinje plexus. One of the principal objects of our investigation was to ascertain, if possible, the location of the muscle activated prematurely by an anomalous route.

The Type Case of Group A.—Depending on the form of the ventricular complex in precordial leads, we have divided our cases into two groups, A and B. Case 1 is the type case of the first group. In this instance, reversion of the anomalous to the normal type of electrocardiogram sometimes occurred spontaneously and could be induced by the ad-

ministration of amyl nitrite. Transitions from excitation of the one sort to excitation of the other were recorded in a variety of leads. In the standard limb leads the normal beats (labeled *n*) are represented by deflections of the kind often seen in the electrocardiograms of healthy young subjects (Fig. 1). In Lead I the QRS complex displays relatively small R and S components, and in Leads II and III it consists of a small Q wave followed by a tall R wave. The mean electrical axis of this complex has a nearly vertical direction, suggesting that the angle made by the long axis of the heart with the long axis of the trunk was a small one. The T waves are inverted in Lead III, as is often the case in electrocardiograms of this type. The anomalous beats (labeled *a*) are represented by patterns of very different form. Apart from the brevity of the P-R and the broadening of the QRS interval, there is conspicuous basal slurring of the first QRS component, and the mean electrical axis of QRS is nearly horizontal. The T deflections are inverted in Lead I. Normal complexes were recorded in only one of the unipolar limb leads, Lead V_F; in this lead they have the same outline as in Leads II and III. The anomalous complexes of Lead V_R show pronounced slurring of the first part of the large initial Q wave, and in Lead V_L the initial R deflection is deformed in a similar way.

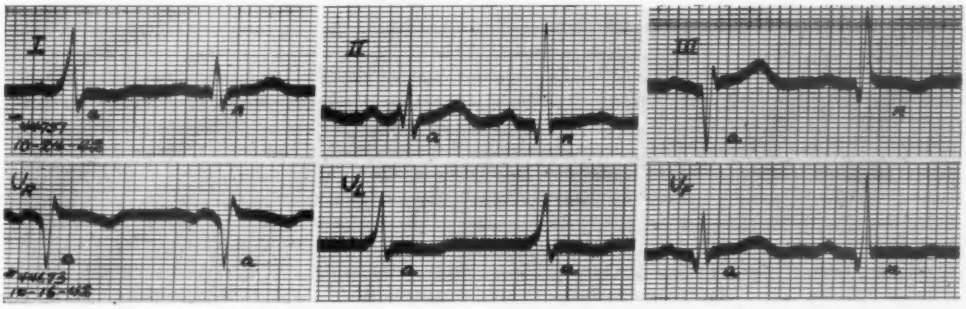

Fig. 1.—Case 1. Standard and unipolar limb leads. Complexes which represent anomalous atrioventricular conduction are labeled *a*, and complexes of the normal type are labeled *n*.

In Fig. 2, five unipolar precordial leads, a unipolar lead from a point overlying the spinal process of the eighth dorsal vertebra (D_{VIII}), and unipolar leads from four levels of the esophagus are reproduced. In the precordial leads the normal beats (labeled *n*) are represented by deflections of the usual type. In Leads V_1 and V_2 the R deflection is small, the R peak falls early in the QRS interval, and S is large; in Lead V_5 the R deflection is large, the summit of this deflection comes later, and small Q and S waves are present. In Leads V_3 and V_E the R and S deflections are approximately equal in size; we may speak of these leads as from the transitional zone. In all of these precordial leads the QRS complex of the anomalous beats (labeled *a*) is dominated by an R deflection which is considerably taller than the R wave of the normal beats and displays pronounced slurring of the basal part of its ascending

limb. The S component of the anomalous and that of the normal QRS complex are largest in the same lead (V_2). The former is small in the leads from the left side of the precordium and the lead from the ensiform process. In Lead V_1 a broad, bifid R wave is the only QRS component. The Q deflection of the normal complex of Lead V_5 does not occur in its anomalous companion. The differences between the T waves of the two kinds of ventricular complexes are as great as the differences between the QRS deflections. The long Q-T interval in Lead V_1 seems to be due to the fusion of a large U wave with the terminal part of T.

In the lead from the auricular level of the esophagus (Lead E_{29}), the difference in length between the P-R interval of the anomalous and that of the normal beats is especially conspicuous. The auricular and ventricular complexes of the latter are of the kind usually seen in unipolar leads from this region. The anomalous complexes are similar in general outline, but the QRS interval is much longer, the descending limb of QS has a much more gradual slope, and the T wave is upright. In the esophageal lead from a point 6 cm. farther from the nares (Lead E_{35}), the initial, slurred part of the QRS complex is still below the isoelectric line, whereas, in the leads from still lower levels (Leads E_{41} and E_{51}), this premature component is positive. The normal ventricular complexes of these last leads are very similar to, and the anomalous complexes very different from, those of the same species in Lead V_5. The deflections of Lead E_{51} are like those of Lead E_{41}, except that the anomalous beat displays a conspicuous R′ which follows the onset of P by approximately the same interval as the R summit of the normal beat. When the long axis of the heart occupies a relatively vertical position, leads from these levels of the esophagus (12 cm. or more below the level

TABLE I

CASE 1. INTERVALS IN FIG. 2. MEASUREMENTS IN SECONDS

LEAD	1		2		3		4	
	a	n	a	n	a	n	a	n
V_1	.093	.124	*{.138 .171	.139	–	.161	.191	.199
V_2	.101	.142	.166	.166	.188	.186	.220	.225
V_3	.096	.145	.172	.171	.202	.196	.220	.196
V_5	.085	.110	.153	.149	.175	.170	.195	.196
V_E	.097	.147	.181	.182	.203	.198	.225	.220
D_{V111}	.068	.132	–	.173	.152	.153	.209	.199
E_{29}	.059	.128	–	.191	.154	.159	.190	.191
E_{35}	.071	.121	–	.166	.142	.142	.201	.183
E_{41}	.105	.135	.131	.174	.154	†{.147 .198	.207	.198
E_{51}	.117	.135	*{.139 .180	.175	‡{.162 .202	†{.147 .202	.220	.214

Key:
a—anomalous; n—normal.
Column 1—interval from beginning of P to beginning of QRS.
Column 2—interval from beginning of P to peak of R.
Column 3—interval from beginning of P to peak of Q, QS, or S.
Column 4—interval from beginning of P to end of QRS.
*Two R peaks present.
†First measurement to peak of Q, second to peak of S.
‡Two S peaks present.

where large diphasic or multiphasic P complexes are obtained) ordinarily yield ventricular deflections like those of leads from the left side of the precordium, and may, therefore, be considered semidirect leads from the surface of the left ventricle. It will be noted that the complexes of the unipolar dorsal lead (Lead D_{VIII}) closely resemble those of Lead E_{35}.

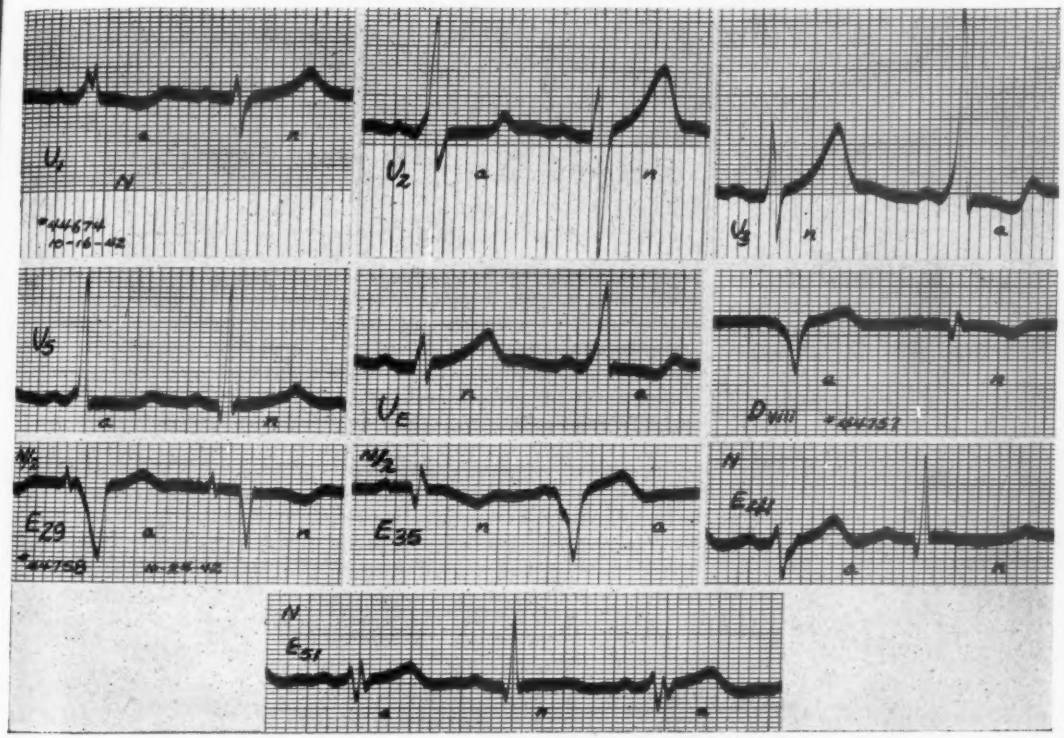

Fig. 2.—Case 1. Precordial Leads V_1, V_2, V_3, V_5, and V_E. A unipolar lead from the region of the eighth spinal process (D_{VIII}). Four unipolar esophageal leads; these leads are labeled E, followed by a number which gives the distance (in centimeters) of the exploring electrode from the nares. Complexes labeled *a* are anomalous, those labeled *n*, normal. In this and in subsequent figures the symbol *N* indicates that the lead was taken with the electrocardiograph at the normal sensitivity (1 cm. equals 1 mv.) the symbol *N/2* indicates that the sensitivity was reduced to one-half the normal (1 cm. equals 2 mv.).

Despite these great differences in form between the normal and the anomalous ventricular complexes, measurements show that in many leads the two types of QRS groups are structurally related. We have already mentioned that the interval from the beginning of the P wave to the end of the QRS complex (the RS-T junction) is of the same length when atrioventricular excitation is anomalous as when it is normal. Measurements of the curves of Fig. 2 are in accord with this statement, and also show that the corresponding peaks of the chief QRS components of the two kinds of curves usually occur at approximately the same time in relation to the P wave. Table I gives, for each of the leads shown in Fig. 2, the intervals from the onset of P to (1) the onset of the initial

QRS component, (2) the peak of R, (3) the peak of the chief downward deflection (Q, QS, or S), and (4) the RS-T junction.

This table indicates that the anomalous P-R interval is certainly more than 0.02, and probably more than 0.05, second shorter than the normal P-R interval in this case. The largest difference was found in the lead from the auricular level of the esophagus, where it amounted to nearly 0.07 second. In Leads V_2, V_3, V_5, and V_E the R peaks of the paired complexes occur at the same time, within a few thousandths of a second, in relation to auricular events. In Lead V_1 the first peak (0.138) of the bifid R of the anomalous complex corresponds to the R summit (0.139) of the normal complex. In Lead E_{41} the R peaks of the two kinds of complexes do not correspond (0.131 and 0.174), and evidently differ in origin. In Lead E_{51} the normal R deflection corresponds in time not to the initial R, but to R′ of the anomalous complex. The paired intervals of the third column of Table I, which give the times of the apices of the largest negative QRS deflections, are in good agreement. In the case of Lead E_{41}, the apex of the anomalous S (0.154) corresponds more nearly to the apex of the normal Q (0.147) than to that of the normal S (0.198). The paired intervals of the last column, which give the time of the RS-T junction in relation to the beginning of P, are also alike except in two or three instances (Leads D_{VIII}, E_{35}, and E_{41}), in which the end of one or both of the QRS complexes is poorly defined.

These measurements clearly support the view that the excitatory process reached the epicardial surface of the anterior wall of the left ventricle at the normal time (in relation to auricular events) and by the normal route, even when some parts of the ventricular myocardium were activated prematurely by an anomalous mechanism. We cannot regard it as fortuitous that the R peak of the anomalous and that of the normal QRS complex of the leads from the left side of the precordium are separated from the beginning of the P wave by the same interval. It is clear, then, that the premature component of the anomalous QRS complex of these leads cannot be ascribed to forces produced by premature excitation of the anterior wall of the left ventricle. As regards the significance of this component in the leads from the right side of the precordium, the situation is similar. There is no evidence that the anterior wall of the right ventricle was activated prematurely. In Leads V_2 and V_E the single R peak of the anomalous, and that of the normal, beat bear the same relation to the P wave. This is likewise true of the first R summit of the anomalous, and the R peak of the normal, QRS complex in Lead V_1. The second R summit of this lead, which is somewhat like that seen in right bundle branch block, cannot be attributed to activation of the anterior wall of the right ventricle unless we suppose that the cardiac impulse reached the epicardial surface in this region abnormally late. This supposition would imply that the

right branch of the His bundle was not functioning, and is not supported by the character of the ventricular complexes of the other leads.

A complete set of the esophageal leads, taken when the cardiac mechanism was continuously anomalous, is reproduced in Fig. 3. The premature component of QRS is inconspicuous in Lead E_{15}; in Leads E_{18}, E_{21}, E_{24}, E_{27}, E_{29}, and E_{33} it is negative, and in the last four of these leads it is conspicuously large. The brevity of the P-R interval in the leads in which this component is largest is apparently due chiefly to the comparatively large magnitude of its earlier fractions; in some of the other esophageal leads these are inconspicuous or isoelectric. In Leads E_{36}, E_{39}, E_{42}, E_{45}, and E_{51} the premature component is positive and relatively small. It will be observed that the QRS complexes of the leads from the highest levels of the esophagus are the inverse of QRS complexes of the leads from the lowest levels. We have already noted that the latter display both an R and an R′ deflection, and are very different in form from the normal complexes of the same leads and from the anomalous complexes of the leads from the left side of the precordium.

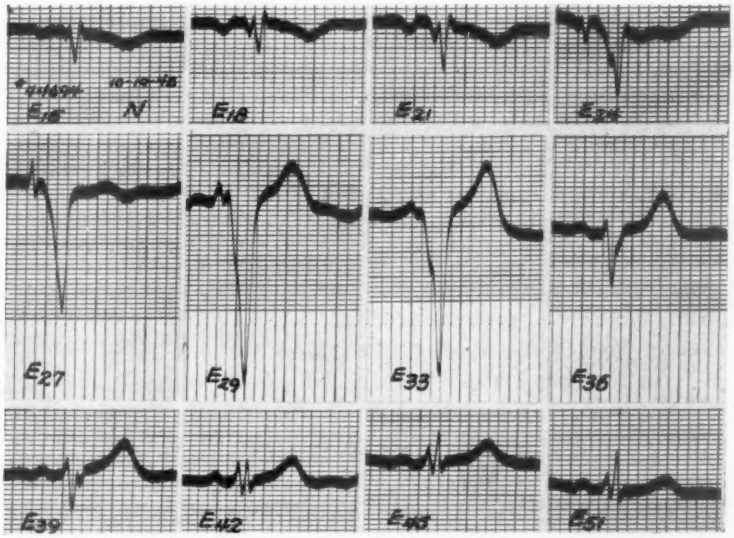

Fig. 3.—Case 1. Esophageal leads. The number which follows *E* gives the distance (in centimeters) of the exploring electrode from the nares.

Unipolar leads from the back and the anterolateral aspect of the right side of the thorax are shown in Fig. 4. The premature component of QRS is clearly negative in the leads from the eighth dorsal spine (D_{VIII}), the right posterior axillary line (RPAL), the right midaxillary line (RMAL), and the right anterior axillary line (RAAL). It is clearly positive in the leads from the left midaxillary line (V_6), the left posterior axillary line (LPAL), the left scapular line (LScL), and a line midway between the right sternal margin and the right midclavicular

line (V_{3R}).* In the lead from the right midclavicular line (RMCL) the premature component is isoelectric. All of these leads were taken from points at the level of the cardiac apex.

In this instance the muscle activated prematurely must have been in the dorsal wall of the heart near the ventricular base, or in the neighboring part of the ventricular septum. This conclusion is supported by the following considerations:

a. The orientation of the electrical forces generated by the heart during the premature fraction of the QRS interval indicates that throughout that period the excitatory process was spreading from the dorsal toward the ventral, and from the basal toward the apical, parts of the myocardium. In this part of the cardiac cycle the potential of the auricular and subauricular† levels of the esophagus and that of a zone extending from the eighth dorsal spine around the right side of the chest to the right anterior axillary line were negative, whereas the potential of the ventricular levels of the esophagus and that of a zone extending from the right parasternal line across the precordium and around the left side of the chest to the left scapular line were positive.

b. The earliest fractions of the premature component of QRS are most conspicuous in the leads from the auricular and subauricular levels of the esophagus. This, together with the relatively large size of this component as a whole in these leads, suggests that when they were taken the exploring electrode was near the region where premature activation began. We believe, in other words, that this component is large in these leads for the same reason that the auricular deflections are large in them.

c. It has been pointed out that in all of the precordial leads the R wave of the anomalous is taller than that of the normal QRS complex. The anomalous QRS group has a net area that is algebraically larger, and the anomalous T complex a net area that is algebraically smaller, than that of the corresponding subdivision of the normal ventricular complex. In the esophageal leads the reverse is the case. This clearly indicates that anomalous excitation increased the number of muscle units activated in a dorsoventral direction.

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*Leads from points on the right side of the chest similar in location to the points from which the standard precordial leads are taken are conveniently differentiated from these by adding R to the subscripts of the standard symbols of the leads to which they correspond.

In normal subjects and in cases of right ventricular hypertrophy, left ventricular hypertrophy, right bundle branch block, and left bundle branch block, the ventricular complexes of unipolar leads from the left posterior axillary line and the left scapular line (at the level of the cardiac apex) are usually similar to those of the leads from the left side of the precordium. Exceptions to this general rule occur in those cases in which the transitional zone is displaced to the left. In these the leads from the left side of the precordium display complexes intermediate in form between those of the leads from the right side of the precordium and those of the leads from the left back. The ventricular complexes of the latter are then like those usually seen in Leads V_5 and V_6 in the type of heart disease present. As a general rule the ventricular complexes of the leads from more lateral parts of the right anterior chest wall are similar to those of Lead V_1; exceptionally, they are like those usually present in this lead in cases of the kind being studied. The deflections of the leads from the right back are variable in form, but often resemble those of Lead V_R. The QRS complex is ordinarily minus-plus diphasic. In right ventricular hypertrophy the second phase usually has the greater voltage, and in left ventricular hypertrophy the first phase usually has the greater voltage. In right bundle block the second component is often very broad. In left bundle branch block the first or negative phase is usually the larger, and the second or positive phase may be absent.

†Less than 10 cm. below the point at which the largest auricular deflections were recorded.

d. The form of the QRS deflections in the leads from the lower subauricular and the higher ventricular levels of the esophagus suggests that the parts of the dorsal ventricular wall nearest the exploring electrode were activated earlier when excitation was anomalous than when it was normal (Fig. 2). In Lead E_{35} the normal QRS group displays a final R deflection; in the anomalous beat, R is wholly lacking. In Lead E_{41} the normal beat exhibits a prominent Q and a late R peak, whereas in the anomalous complex R is small and its peak falls in the premature part of the QRS interval (Table I). In Lead E_{51} the situation is similar except that here the anomalous QRS complex has an R′ in addition to the initial R wave. This R′ summit comes at the same time as the normal R peak of the same lead. Fig. 3 shows that it is embryonic in Lead E_{39} and progressively larger in the leads from lower levels, which suggests that it represents the response of some of the lowest portions of the dorsal ventricular wall to the normal excitation wave. The leads from the left back (Fig. 4, LPAL and LScL) exhibit QRS deflections of similar form, whereas the QRS complex of these leads is normally dominated by a late R deflection.

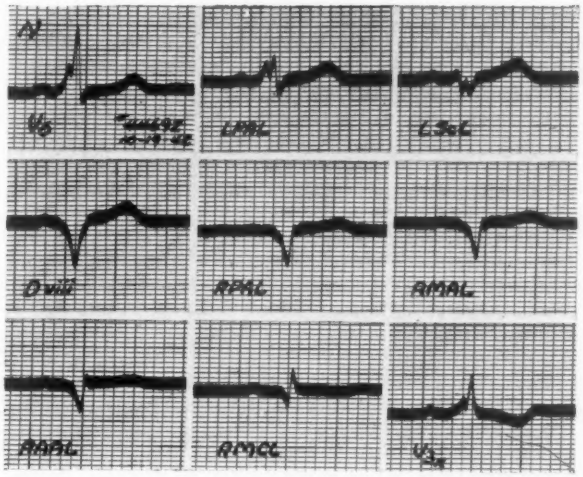

Fig. 4.—Case 1. Unipolar leads from the back and from the anterior right hemithorax at the level (approximately) of the cardiac apex. *LPAL*, left posterior axillary line; *LScL*, left scapular line; D_{VIII}, eighth dorsal spine; *RPAL*, right posterior axillary line; *RMAL*, right midaxillary line; *RAAL*, right anterior axillary line; *RMCL*, right midclavicular line; V_{3R}, halfway between the right midclavicular line and the right sternal margin.

It seems probable that the anomalous excitatory process invaded the subepicardial muscle first, and spread toward the endocardium, but lack of information as to what effects might be produced by dorsoventral activation of septal muscle makes it impossible to be sure that such was the case. The esophageal leads throw no light on the question as to whether the excitation wave spread through the dorsal ventricular wall from without inwards or vice versa. When the premature component of the anomalous QRS complex is negative in one of these leads,

the initial component of the normal complex is likewise negative. Normally, the ventricular cavities are negative throughout the QRS interval, and the initial negative component of QRS in leads from the auricular and subauricular levels of the esophagus is presumably due to the transmission of the potential of the ventricular cavities to these regions. That anomalous atrioventricular excitation gives rise to initial negativity of the left ventricular cavity as a whole seems unlikely, for, in the leads from the left side of the precordium, the premature component of the anomalous QRS complex is positive even when the normal QRS complex displays a conspicuous Q deflection. The evidence bearing upon its effect upon the initial potential of the cavity of the right ventricle is less conclusive. In the leads from the right side of the precordium the premature component of the anomalous QRS complex is positive in Case 1, but not in all the other cases of our series. It would seem that positivity of this component in all of the standard precordial leads must be due to activation of the dorsal ventricular wall from without inwards or to dorsoventral activation of septal muscle, if we are warranted in excluding premature activation of the anterior ventricular wall on the grounds previously mentioned.

The occurrence of a second R summit in the anomalous QRS complex of Leads V_1 and V_{3R} is not easy to explain satisfactorily. If the first R summit, which corresponds, as regards its relation to P, to the normal R peak, marks the completion of the excitation of the anterior wall of the right ventricle by impulses arriving via the His bundle, the later fractions of the bifid R wave must be of septal origin in the sense that they represent the overbalancing of opposing forces by those generated by the activation of septal muscle in a left to right direction. In the leads from the left back and the left axilla, an S deflection occupies this same part of the QRS interval, and it is apparent that this deflection and the second R summit in question have the same origin. It seems likely that abnormally early activation of parts of the posterior and posterolateral wall of the left ventricle by the anomalous excitation process prevented the development in these regions of those electric forces which, late in the QRS interval, normally opposed the septal forces referred to.

It may be pointed out here that our observations are not in accord with any of those hypotheses which attribute the electrocardiographic features of the syndrome under consideration to an anomaly of conduction or of impulse formation affecting the right or left branch of the His bundle. An anomaly of this kind should give rise to a QRS pattern characteristic either of complete or of incomplete bundle branch block. Left bundle branch block decreases the size of the R deflection and enormously increases the area of the S wave in the leads from the right side of the precordium. Right bundle branch block does not greatly change the height of the R wave, but substantially decreases the net area of QRS in the leads from the left side of the precordium. It does not abolish Q waves in these leads in cases in which they are present when

the ventricles are activated in the normal way. We feel sure, therefore, that an anomaly of the kind specified could not give rise to electrocardiograms of the kind reproduced in Fig. 2.

Classification of Cases; Groups A and B; the Electrical Axis.—As regards the form of the anomalous ventricular complex in certain leads, all the cases of our series are very much alike. With respect to the form of this complex in other leads, there are great differences between them. The leads from the left side of the precordium, particularly Leads V_4 and V_5, belong to the first class (Figs. 2, 6, 9, and 11). The anomalous QRS complex of these leads is always dominated by a large R wave, and the basal part of the ascending limb of this deflection is invariably slurred or notched by a positive premature component. In most instances there is also a small S wave in one or both of the leads mentioned, but Q is never present in either. In Lead V_6 the ventricular deflections have essentially the same form as in Leads V_4 and V_5, except that the voltage of R is almost always smaller, on occasion much smaller, as in Cases 2 and 4, and S is sometimes considerably deeper (Cases 1, 2, 3, and 4). Depending on the form of QRS in the leads from the right side of the precordium, particularly Leads V_1, V_2, and V_E, our cases have been divided into two groups: Group A, in which R is the sole, or by far the largest, deflection in all of these leads, and Group B, in which S or QS is the chief QRS deflection in at least one of them. Cases 1, 2, 3, 4, and possibly 7 fall in Group A (Figs. 2, 6, and 11), and Cases 5, 6, 8, and 9 fall in Group B (Figs. 9 and 11); Case 10, in which the form of QRS in these leads varied greatly, will be discussed separately. In the four cases in which esophageal leads were taken, the QRS complexes of the leads from the auricular and subauricular levels have essentially the same outline (Figs. 2, 3, 8, and 16). With one exception (Case 1), the ventricular deflections of the leads from the lowest levels of the esophagus are like those of the leads from the left side of the precordium. Leads from the back and the anterolateral aspect of the right side of the chest were taken in Cases 1, 3, 4, 8, and 10. In all of them the lead from the eighth dorsal spine exhibits a broad QS deflection similar to that seen in the leads from the auricular levels of the esophagus (Figs. 4, 7, and 8). The QRS complexes of the lead from the left scapular line resemble those of the leads from the left side of the precordium in only one instance. In most normal subjects, in bundle branch block, and in ventricular hypertrophy the complexes of the leads from the left back and those of the leads from the left side of the precordium are usually strikingly similar in form.

As to the limb leads, there are pronounced variations in the form of the ventricular complexes of Leads V_L and V_F, and therefore in the position of the electrical axis from case to case, but in Lead V_R the QRS deflections have approximately the same general outline in all instances (Figs. 1, 5, and 10). Left axis deviation is very common in anomalous

atrioventricular excitation, and the electrocardiograms in half of our series of ten cases exhibit it. In the three cases of these five in which reversion of the anomalous ventricular complexes to the normal form was recorded in the limb leads, the mean electrical axis of the normal

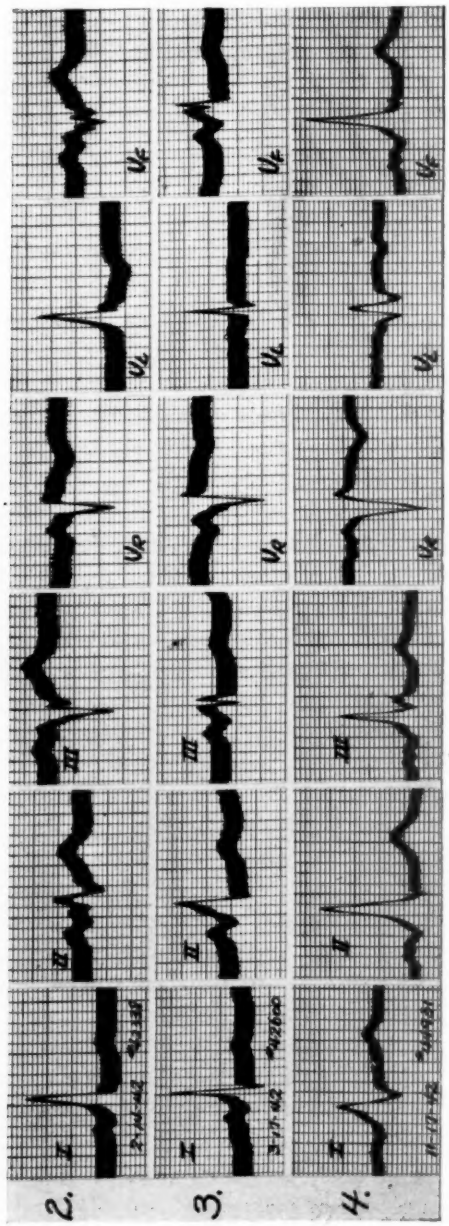

Fig. 5.—Cases 2, 3, and 4. Standard and unipolar limb leads.

QRS group is nearly vertical. It is clear, therefore, that the factors responsible for left axis deviation when the cardiac mechanism is anomalous are not the same as those that give rise to it when the cardiac

mechanism is normal. In Case 1 the anomalous QRS deflections of Lead V_F (Fig. 1) resemble those of the leads from the ventricular levels of the esophagus (Fig. 3), although the initial R wave (not present in the strip of Lead V_F reproduced, but well marked in tracings taken on other occasions) is much larger in the esophageal leads. In Case 8 the ventricular deflections of Lead V_F (Fig. 10) are like those of the leads from the right side of the back (Fig. 7), and, in Case 6 (Fig. 10), like those of esophageal Lead E_{47} (Fig. 8). In these same cases, the QRS deflections, although not the T waves, of Lead V_L are more like those of the leads from the left side of the precordium. It seems probable, therefore, that the occurrence of left axis deviation was due in these cases to abnormally early excitation of the more basal parts of the dorsal ventricular wall and the transmission of the potential variations of this region to the left leg as in posterior myocardial infarction. In those instances in which the limb curves do not display left axis deviation, the ventricular complexes of Lead V_F are like those of the leads from the left side of the precordium or those of the leads from the lowest levels of the esophagus (Case 4, compare Lead V_F, Fig. 5, and Lead E_{59}, Fig. 8). Whether these cases differ from the others because the long axis of the heart made a more acute angle with the frontal plane, or for some other reason, is not clear. It should be noted that there is no correlation between the inclination of the mean electrical axis of QRS in the limb leads and the form of the anomalous ventricular complex in the leads from the right side of the precordium; left axis deviation occurs in cases that belong to Group A (Case 1, Fig. 1), as well as in those that belong to Group B (Case 8, Fig. 10). Our observations suggest, however, that cases of the first group are more likely to display prominent S waves in Lead I and in the leads from the extreme left side of the precordium than are those of the second.

Additional Cases of Group A; Comparison With the Type Case.— Cases 2, 3, 4, and 7 are members of Group A, and may be compared with the type case of this group which has been discussed at length. The anomalous ventricular complexes in Case 2 differ from those in Case 1 in the following respects: there is no S deflection in either Lead I or Lead V_L (Fig. 5); the R wave of Lead V_1 is less distinctly bifid; there is no S deflection in any of the precordial leads except Lead V_6, and the R wave of this lead is very small (Fig. 6).

In Case 3 the limb leads do not show left axis deviation (Fig. 5), and the R wave of Lead V_1 has only one peak (Fig. 6). Two sets of curves were taken in this case, the first on March 17, 1942, before splanchnicectomy, and the second on Aug. 17, 1943, after this operation. The extremity and precordial leads reproduced here belong to the first set, and the other thoracic leads, to the second set. The differences between the two sets of tracings are of a minor kind. Compared to the first, the second set of precordial curves exhibits a larger S wave in Leads V_1 and V_F, smaller R deflections in Leads V_2 to V_6, inclusive, and upright in-

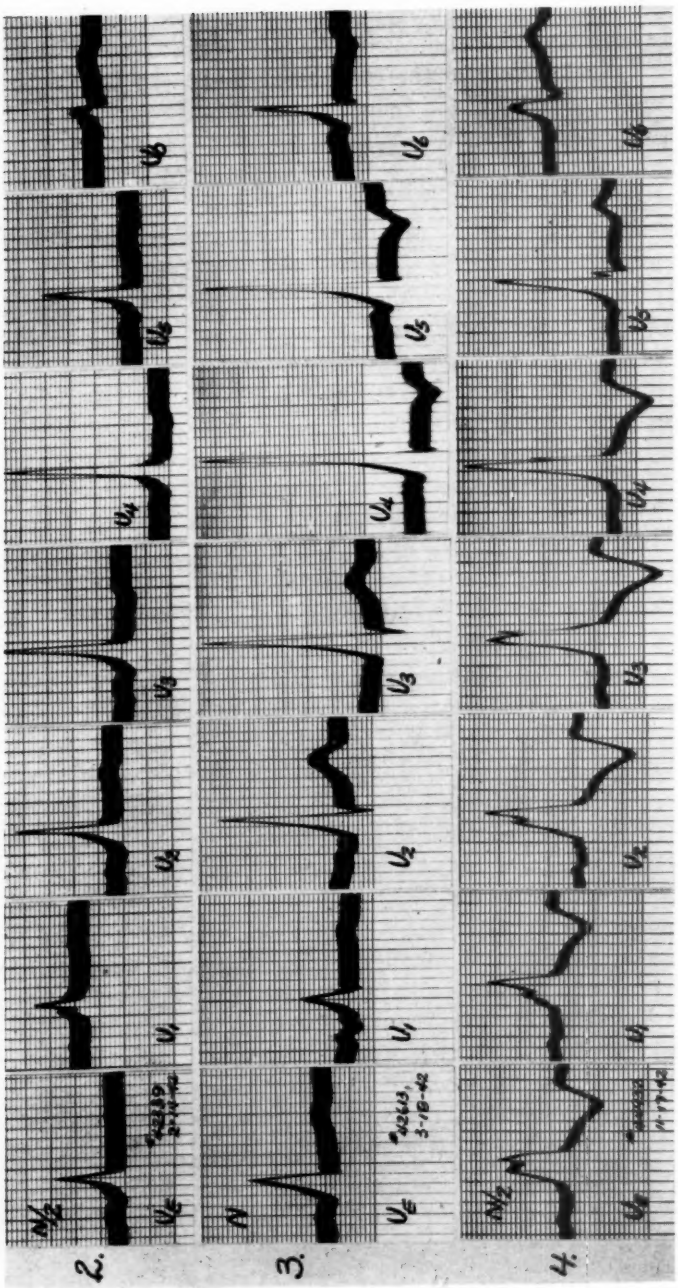

Fig. 6.—Cases 2, 3, and 4. Precordial leads.

stead of inverted T waves in Leads V_4, V_5, and V_6. The first set of leads from the back, the right axilla, and the right anterior chest wall differs from the second set in these particulars: there is a distinct S deflection in the lead from the left posterior axillary line, the T wave in this lead is inverted instead of upright, and there is no S in Lead V_{3R}.

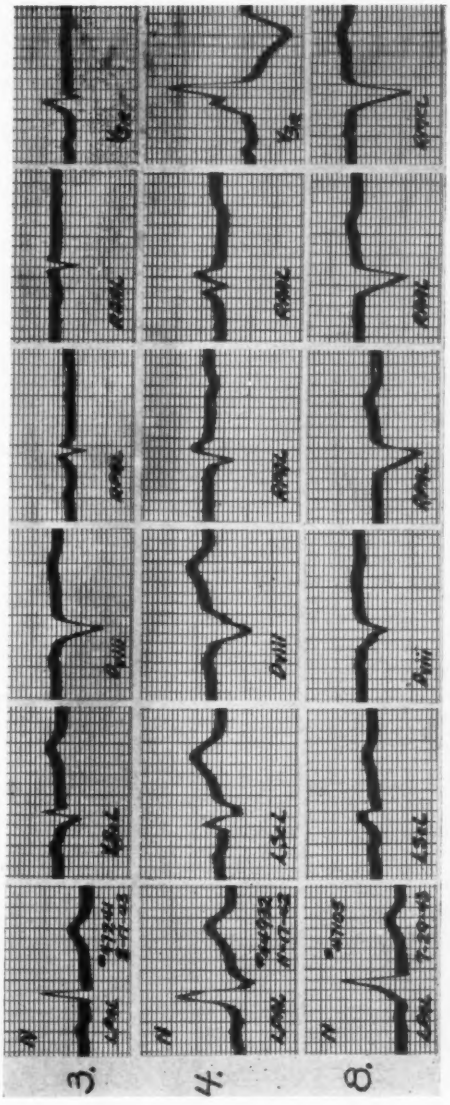

Fig. 7.—Cases 3, 4, and 8. Unipolar leads from the back and right anterior hemithorax. Compare with Fig. 4, in which the same symbols are employed.

In Case 7 precordial leads were taken on three occasions, June 19, 1934, July 9, 1934, and July 27, 1934. The second set of curves is reproduced (Fig. 11). In the others the ventricular complexes of Lead V_E have the same form, but those of Lead V_1 display a conspicuous S wave. In the third set this S is as large as the R wave, and there is some

doubt as to whether this case properly belongs in Group A. In the figures it has been placed with the cases of Group B.

In Case 4 precordial leads were taken Nov. 13, 1942, as well as on Nov. 17, 1942. There are no significant differences between the two sets of tracings. The form of the ventricular deflections of the standard leads, however, was quite variable, and could be greatly modified by forced respiration. There was always a prominent S wave in Lead I,

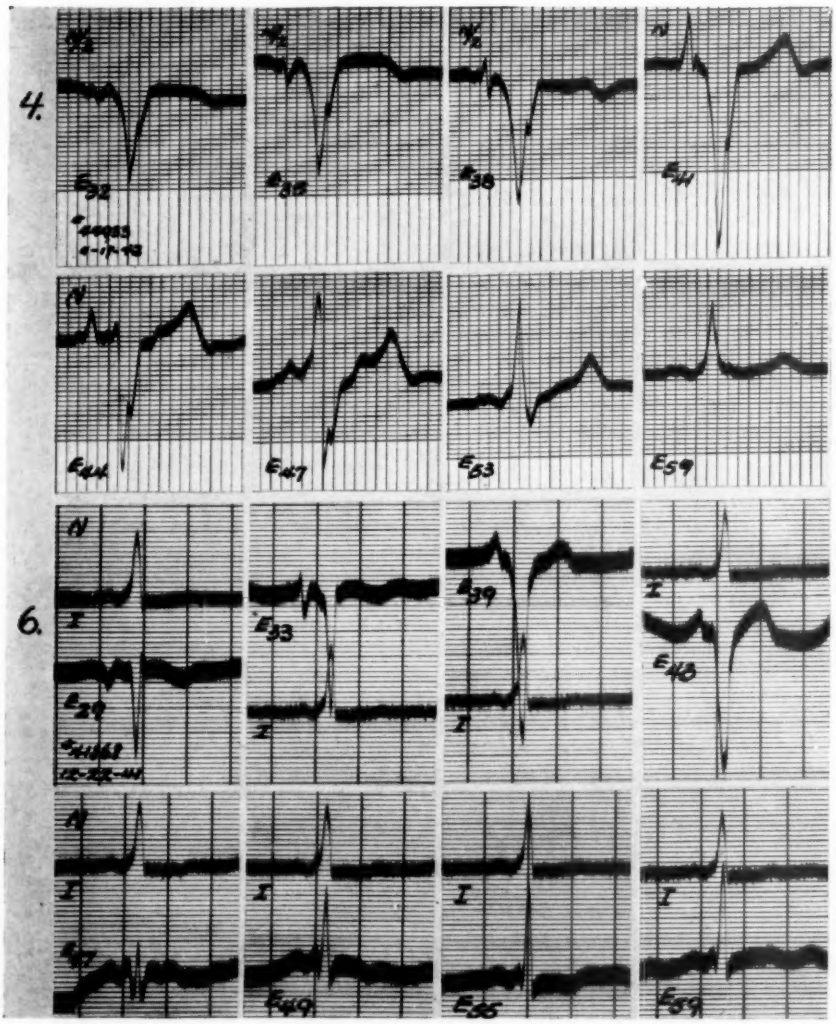

Fig. 8.—Cases 4 and 6. Unipolar esophageal leads. Compare with Fig. 3.

but in some records the voltage of R_1 is more than twice as great as in that reproduced (Fig. 5). The very long QRS interval, which measures at least 0.16 second, and the broad, deformed P waves of the limb leads raise the question as to whether anomalous atrioventricular excitation

was the only cardiac abnormality present. The ventricular complexes of the thoracic and esophageal leads differ from those of the corresponding leads in the type case in minor particulars only (Figs. 6, 7, and 8). The premature component of QRS is positive instead of negative in the leads from the right anterior axillary line, and there is a more conspicuous final R deflection in the leads from the right back (Fig. 7). In the leads from the lowest levels of the esophagus (Fig. 8) there is only one R wave and this component is much larger than in Case 1 (Fig. 3).

The Type Case of Group B.—Case 5 is a typical example of the cases of the second group. In this instance transitions from the normal to the anomalous cardiac mechanism could be induced by the Valsalva procedure. Strips of the standard extremity leads and the unipolar precordial leads which show both kinds of ventricular complexes are reproduced in Fig. 9. No other leads were taken. Both the normal and the anomalous ventricular complexes of the limb leads closely resemble the corresponding complexes of the same leads recorded in Case 1. It will be noted, however, that in Lead I there is no S component in either species of complex, whereas, in Case 1, there is a conspicuous S in both (Fig. 1). There are no significant differences between the type cases of the two groups as far as the deflections of the leads from the left side of the precordium are concerned, with one possible exception. In Case 1 there is a conspicuous S wave in the anomalous QRS group of Lead V_6; in Case 5 this component is absent. On the other hand, the two cases differ greatly as regards the form of the anomalous ventricular complexes of the leads from the right side of the precordium (V_1 and V_2). In Case 5 the premature component is diphasic in Lead V_1 and very small in Lead V_2. There is a notch on the descending limb of the deep S wave of these leads. There is no trace of the final positive com-

TABLE II

CASE 5. INTERVALS IN FIG. 9. MEASUREMENTS IN SECONDS

	1		2		3		4		5	
LEAD	a	n	a	n	a	n	a	n	a	n
I	.122	.160	–	.173	.203	.203	–	.227	.244	.238
II	.115	.155	–	.170	.204	.204	.230	.237	.256	.251
III	.121	.152	.170	.170	.196	.202	.216	.234	.250	.248
V_1	.116	.150	–	–	.144 .182*	.175	.206	.204	.256	.244
V_2	.116	.166	–	–	.146 .187*	.192	.216	.222	.261	.262
V_3	.127	.172	–	–	.216	.210	.251	.232	.268	.266
V_4	.129	.171	–	.171	.211	.215	.250	.231	.257	.253
V_5	.128	.163	–	.171	.212	.204	.246	.228	.258	.252
V_6	.119	.155	–	.166	.206	.200	–	.238	.252	.232

Key:
a—anomalous; n—normal.
Column 1—measurement from beginning of P to beginning of QRS.
Column 2—measurement from beginning of P to peak of Q.
Column 3—measurement from beginning of P to peak of R.
Column 4—measurement from beginning of P to peak of S.
Column 5—measurement from beginning of P to end of QRS.
*Measurement to submerged R peak on descending limb of S.

ponent which is such a prominent feature of the anomalous QRS of Lead V_1 in the type case of Group A. It may be pointed out, however, that in Leads V_1 and V_2 the net area of the anomalous QRS is algebraically larger than the net area of the normal QRS. This is clearly

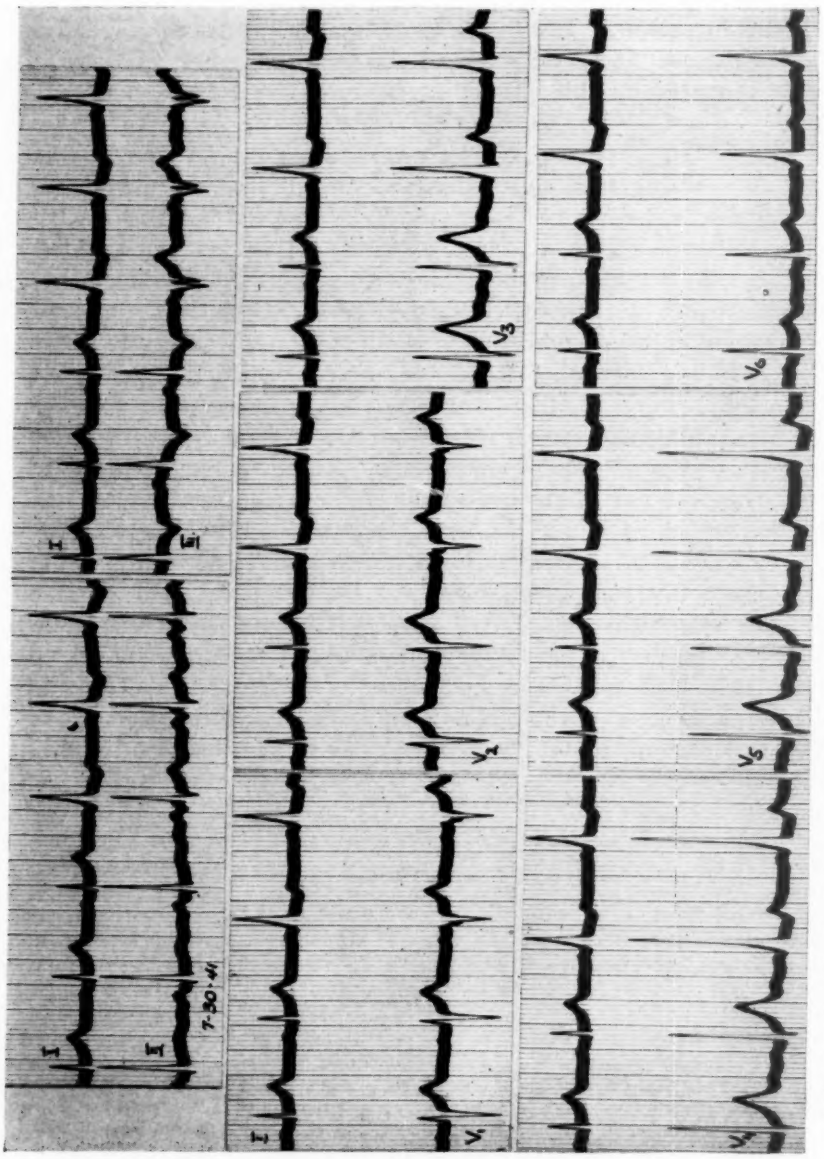

Fig. 9.—Case 5. Leads II and III and precordial Leads V_1 to V_6 inclusive, taken simultaneously with Lead I. In the records of the standard leads, the first three complexes are normal, the last three anomalous; in the precordial leads the first two are normal, the last two anomalous. Compare with Figs. 1 and 2.

indicated by the comparative size of the anomalous and the normal T waves. The difference between Case 5 and Case 1 in this respect is one of magnitude and not one of kind.

Table II gives, for each lead and for each type of complex, measurements of the interval from the beginning of the P wave to (1) the onset of the first QRS deflection, (2) the apex of Q, when this component is present, (3) the apex of R, (4) the apex of S, and (5) the end of the QRS complex. The P-R interval of the anomalous beats appears to be

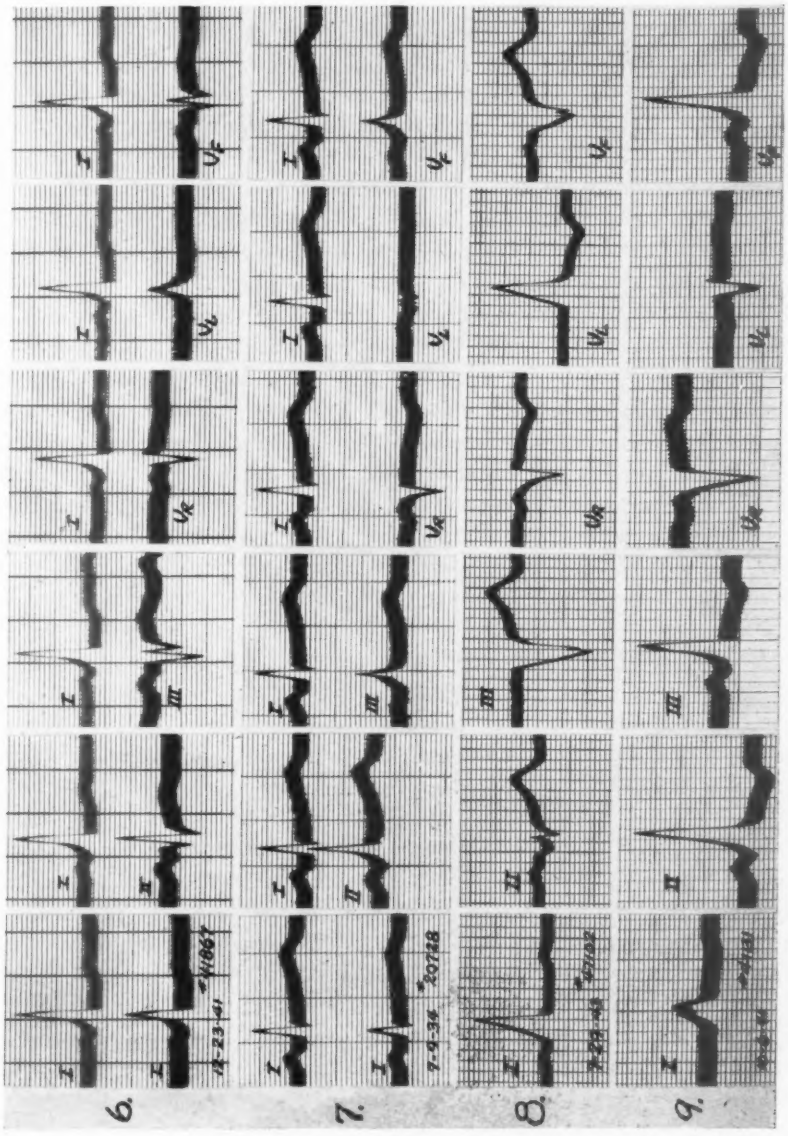

Fig. 10.—Cases 6, 7, 8, and 9. Standard and unipolar limb leads. Compare with Fig. 5.

roughly 0.04 second shorter than that of the normal beats, and the interval from the beginning of P to the end of the QRS complex is approximately the same for beats of both types. In the standard limb leads and in the leads from the left side of the precordium the R peak of the

normal, and that of the anomalous, complex bear the same relation to the P wave within a few thousandths of a second. In the leads from the right side of the precordium the notch on the descending limb of S in the anomalous complex corresponds in time to the peak of R in the normal QRS complex. These measurements, like those of Table I, support the view that the His bundle transmitted impulses when the cardiac mechanism was anomalous as well as when it was normal.

Group B; Additional Cases.—Case 6 is a much less striking example of Group B than that taken as the type. The S deflection is large in Leads V_1 and V_E, and there is no trace of a positive QRS component at the end of the QRS interval (Fig. 11). On the other hand, the premature component of QRS is positive in both of these leads, and there is a small S deflection in Lead V_6. The ventricular complexes of the leads from the lowest levels of the esophagus are similar to those of the leads from the left side of the precordium (Fig. 8).

In Case 8 the premature component is positive in all the precordial leads and there is a trace of a final upward deflection in the QRS complexes of Leads V_1 and V_2 (Fig. 11). There is, however, no S wave in Lead V_6, and the chief QRS deflection is downward in Leads V_1 and V_E. The QRS complexes of the leads from the right back, right axilla, and the right side of the anterior chest wall are quite different from those of the same leads in the cases of Group A (Fig. 7). The premature component is negative in all of these leads, and there is no final R wave in any of them. These differences are mentioned, but since these leads were not taken in any of the other cases of this group, they may not be significant.

In Case 9 there is a very deep QS deflection in Lead V_1, and a deep S deflection in Leads V_2 and V_3 (Fig. 11). The premature component is negative in the first of these leads and positive in the other two. There is no trace of a final R deflection in either Lead V_1 or V_2, and there is no S wave in Lead V_6. This case presents all the characteristics of the group.

It will be noted that there is no S deflection in Lead I in any of the cases of Group B, although the position of the mean electrical axis of the anomalous QRS complex varies greatly from case to case. The absence of a prominent S wave in Lead V_6 is also conspicuous (Figs. 9 and 11). Although we suspect that the muscle on the dorsal wall of the heart that was activated prematurely was smaller in amount or different in distribution in the cases of this group than in those of Group A, there is not enough evidence bearing on this point to justify any conclusion. We must, therefore, consider whether the electrocardiographic differences between the cases of these two groups are dependent upon differences in the order of ventricular activation or upon variations in the position of the heart. The magnitude of the differences, as regards the form of the anomalous ventricular complexes of the leads from the right side of the precordium, between Cases 1 and 4, on the one hand, and Cases 5

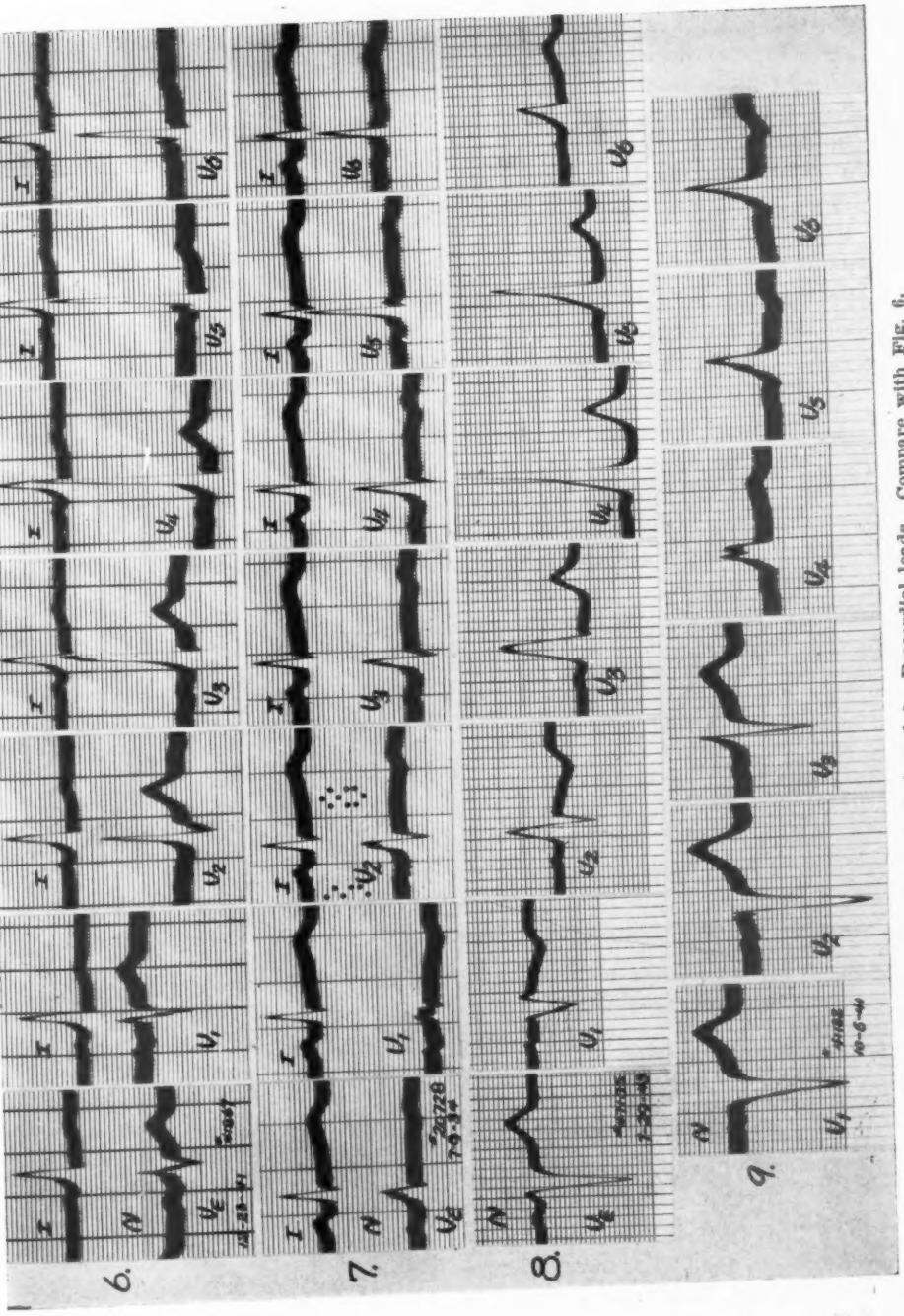

Fig. 11.—Cases 6, 7, 8, and 9. Precordial leads. Compare with Fig. 6.

and 9, on the other, is certainly opposed to the second supposition. This difference is particularly striking when it is borne in mind that, as regards the form of the normal ventricular complexes, Cases 1 and 5 differ only in very minor particulars. We must, however, remember that the effect produced by the position of the heart upon the ventricular deflection must be dependent upon the character of the potential variations on the different aspects of the ventricular surface, and, consequently, that a given change in the position of the heart may give rise to conspicuous changes in the ventricular electrocardiogram, or no changes at all, depending upon the epicardial distribution of potential variations of one kind, as compared to the distribution of those of an opposite sort. On the basis of the data presented, it is not possible to accept or reject either of the two possibilities mentioned, but the observations described in a later section of this article indicate that the differences between the cases of Group A and those of Group B are due, at least in some measure, to differences in the order of ventricular activation.

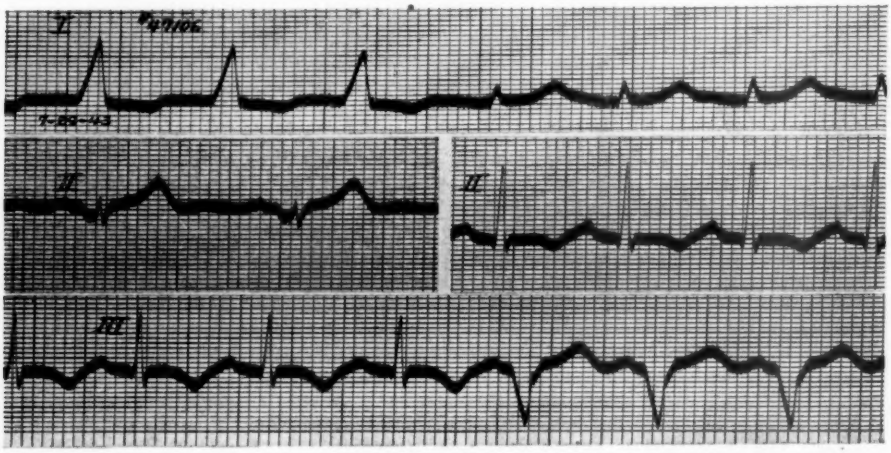

Fig. 12.—Case 8. Leads I, II, and III, showing both anomalous and normal complexes.

OBSERVATIONS RELATING TO THE EFFECT OF ATRIOVENTRICULAR RHYTHM UPON THE FORM OF THE VENTRICULAR COMPLEX IN ANOMALOUS ATRIOVENTRICULAR EXCITATION

An accessory atrioventricular bundle, if it is regarded as a separate and distinct structure, and in no sense as a part of, or as connected with, the specialized atrioventricular system of the normal heart, can hardly transmit the excitatory process from auricles to ventricles when the cardiac rhythm is under the control of a center in the lower levels of the atrioventricular node. Our working hypothesis, then, implies that in cases of anomalous atrioventricular excitation the ventricular complex must assume the normal form on the induction of atrioventricular rhythm of the kind in which ventricular excitation is simultaneous with, or precedes, auricular. We have not made an extensive search of the

literature, but two cases of anomalous atrioventricular excitation in which atrioventricular rhythm of this sort was observed have come to our attention. One of these was reported by Fox, Travell, and Molofsky,[14] and the other by Aixalá.[15] The ventricular complex was of the normal form during the atrioventricular rhythm in both of these cases. The authors who reported them did not comment upon the possible significance of their observations on this point.

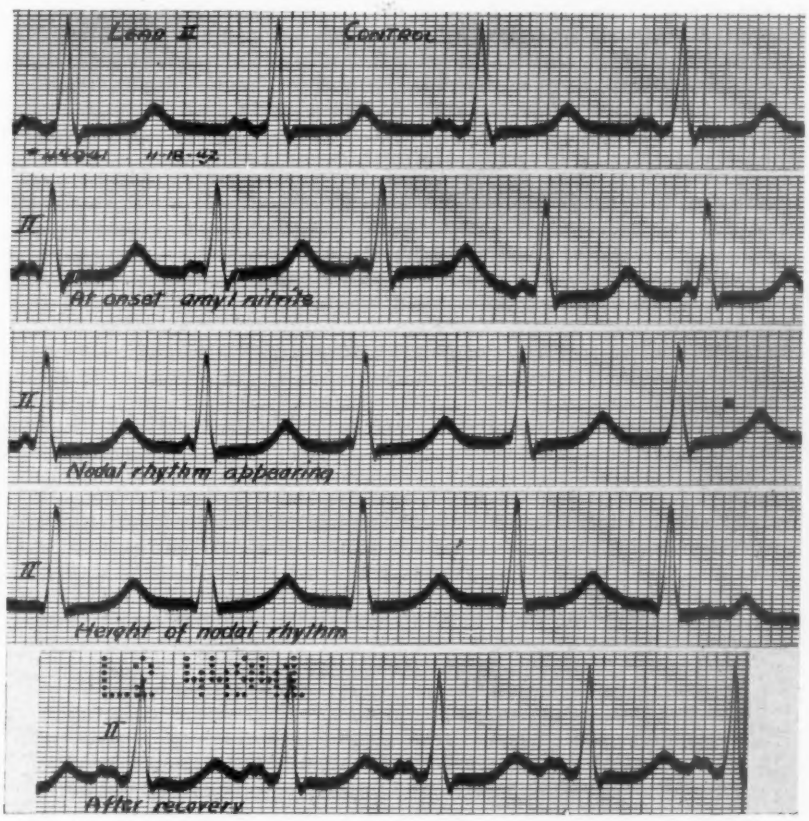

Fig. 13.—Case 4. The effect of atrioventricular nodal rhythm upon the form of the anomalous ventricular complex in Lead II.

In Case 4 of our series, atrioventricular rhythm of the kind in which the P wave is buried in the QRS complex was observed on two occasions. On the first, it appeared when the patient inhaled amyl nitrite approximately three hours after the administration of 0.6 Gm. of quinidine sulfate. Up to that time the latter had had no noticeable effect upon the cardiac mechanism. On the second occasion it was induced by carotid sinus stimulation approximately eight minutes after the hypodermic injection of 0.0013 Gm. of atropine sulfate. Thirty minutes after this injection the same procedure was no longer effective. The occurrence of atrioventricular rhythm after the inhalation of amyl nitrite is illustrated in Fig. 13. In the control record a broad, notched

P wave is followed by a slowly rising segment which is apparently part of the QRS complex. If this interpretation is correct, the QRS interval measures approximately 0.14 second, but if the segment in question is ignored, this interval does not much exceed 0.10 second. The abnormally long Q-T interval may be due to the administration of quinidine. The next two strips of record show a transition from sinus rhythm to atrioventricular rhythm. During this transition the ventricles were responding to the atrioventricular node, but some fraction of the auricular muscle was still responding to the sinus node, for that part of the P wave which remains visible retains its original form. In the fourth strip of record, no part of the P wave can be seen, and we may assume that when this record was taken all of the cardiac muscle was responding to the atrioventricular node. The final strip of record represents the re-establishment of sinus rhythm. The ventricular complexes recorded during the ectopic rhythm differ significantly from those of the control tracing in two respects: they display a somewhat shorter QRS interval and a definite Q deflection. It will be noted that Q did not appear as long as any trace of the original P wave preceded the QRS complex, and the reason for this is obvious. On the other hand, the reduction in the size of S which occurred simultaneously with the appearance of Q is difficult to understand. If it were due to the change in the location of the ventricular pacemaker it should have occurred when the ventricle began to respond to the atrioventricular node. It is probable that the change in the size of this component has no important significance, for it did not occur when atrioventricular rhythm was induced by carotid sinus stimulation after the administration of atropine.

The results of this experiment are somewhat equivocal, for the ventricular complex neither retained its original outline nor assumed an entirely normal appearance when atrioventricular rhythm developed. We have already mentioned reasons for suspecting that anomalous atrioventricular excitation was not solely responsible for all of the electrocardiographic peculiarities in this case. We do not, therefore, feel justified in concluding that the ectopic rhythm failed to abolish those that can be justifiably ascribed to it.

A most interesting case, the last of our series, and one of those studied by Hecht, at the William J. Seymour Hospital, remains to be described. The patient was under observation for a long period, and many electrocardiograms were taken. We shall describe and illustrate only the more significant.

The anomalous QRS complexes of the limb leads (Fig. 15, *a* and *b*) and those of the leads from the left side of the precordium (Leads V_4, V_5, and V_6, Fig. 14) have the same general contour in all records. The former exhibit pronounced left axis deviation, and the latter differ in no significant way from the QRS complexes of the same leads in the other cases of our series. On the other hand, the form of the QRS complexes of the leads from the right side of the precordium is very variable (Fig.

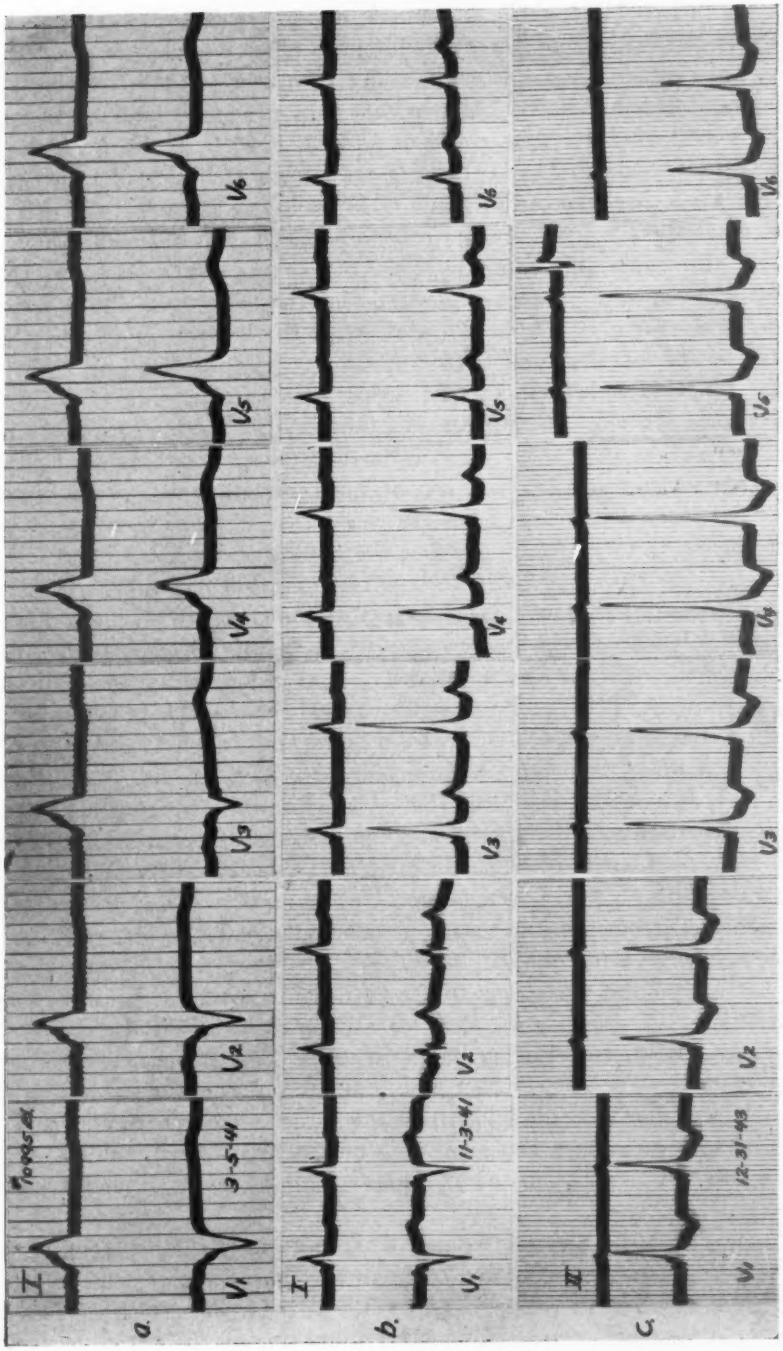

Fig. 14.—Three sets of precordial leads taken simultaneously with a standard limb lead. In *c* the limb lead was taken with the electrocardiograph at subnormal sensitivity. Note variation in the form of the ventricular complexes of the precordial leads.

14). In the tracing taken March 5, 1941, Leads V_1, V_2, and V_3 display large QS deflections, notched in the last of these leads by an embryonic R wave near the end of the QRS interval (Fig. 14, *a*). In the limb leads of the same date the P waves differ from those of the first electrocardiogram, dated Feb. 27, 1941, in that they are small in Lead II and inverted in Lead III. The curves of Nov. 3, 1941 (Fig. 14, *b*), show a large QS deflection in Lead V_1 and a polyphasic QRS complex in Lead V_2. In the other precordial leads QRS is represented by a broad R wave, slurred at the base of its ascending limb. Esophageal tracings taken on the same date show large QS deflections in the lead from the auricular level, and complexes like those of the leads from the left side of the precordium in Leads E_{40} and E_{50}. In the records of Dec. 31, 1943 (Fig. 14, *c*), the chief QRS deflection is upward in all of the precordial leads, including V_E; in the leads from the left side of the precordium the R waves are much taller than in the previous records, and the T waves are inverted. It is unlikely, if not impossible, that these pronounced variations in the form of the ventricular complexes of the precordial leads could have been due solely to variations in the position of the heart or to errors in placing the exploring electrode.

By Dec. 29, 1943, the patient's mental condition had deteriorated to such an extent that it was necessary to administer sodium amytal in a dose of 0.25 Gm. (3¾ grains) to obtain satisfactory electrocardiograms. In some of the records taken on that day, and subsequently, the P deflections are upright in all of the standard limb leads; in others they are inverted in Leads II and III (Fig. 15, *a* and *b*). We shall assume that P waves of the first type represent normal sinus rhythm, and those of the second type, a homogenetic rhythm arising in the upper levels of the atrioventricular node. Whether or not this assumption is justifiable is of no consequence, if it is admitted that the centers responsible for the two rhythms differed in location. Unfortunately, one rhythm can be distinguished from the other only in Lead II, Lead III, or a lead from the auricular levels of the esophagus. We are, therefore, not able to say whether or not the variations in the form of the ventricular complexes exhibited by the records we have already described were due to variations in the location of the cardiac pacemaker. We mention this because other records show clearly that the character of the auricular rhythm exerted an important influence upon the form of the ventricular deflections of the leads from the right side of the precordium. It had only minor effects upon the outline of these deflections in the other leads employed.

On Dec. 29, 1943, a rather extensive exploration of the potential variations of the thorax was carried out. In the limb leads of that date the P wave is inverted in Leads II and III, but it is not certain that atrioventricular rhythm was continuously present during the period required to take all of the many unipolar leads employed. In the leads from the left margin of the sternum, from the left midclavicular line, and from

a line halfway between the two (levels of the second, third, fourth, and fifth intercostal spaces), the QRS deflections are represented by a broad R wave which is slurred near the base of its ascending limb. In the leads from the right sternal margin, the right midclavicular line, and a line midway between the two (levels of the second, third, fourth, and fifth intercostal spaces), the QRS complex consists of a broad QS deflection, or of a Q followed by an R wave, with one notable exception. In

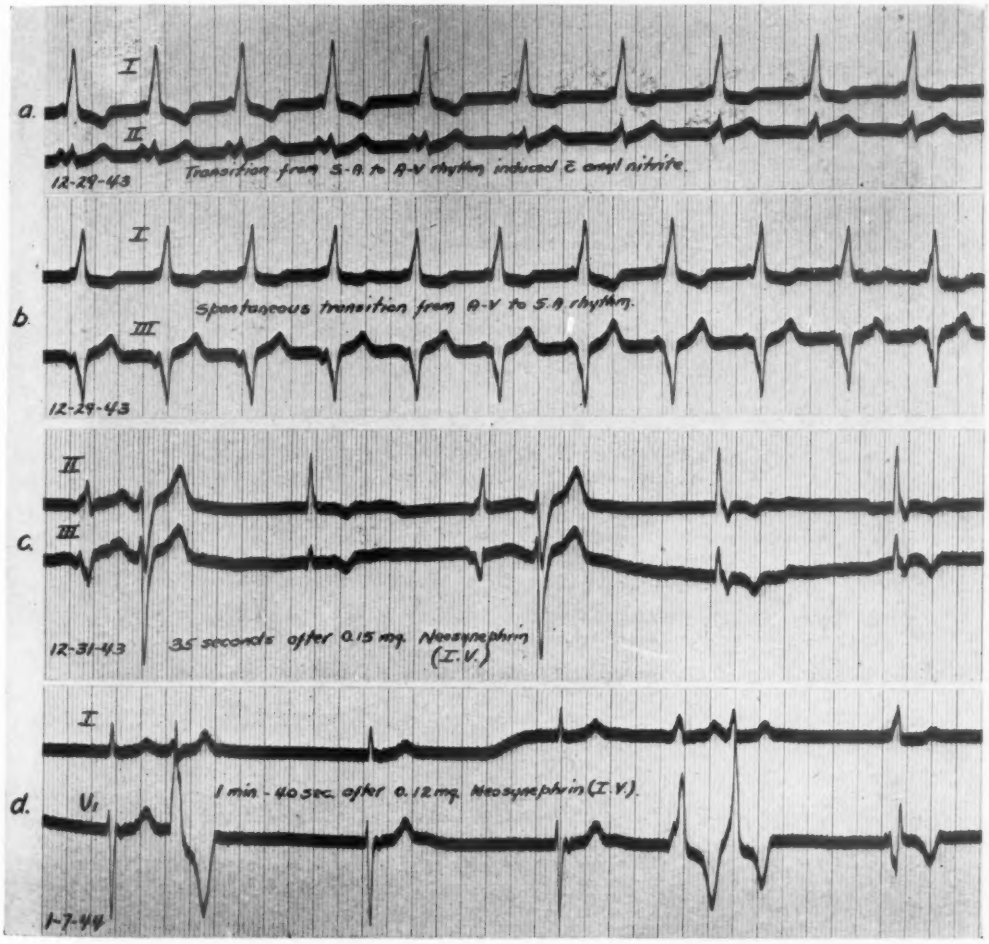

Fig. 15.—Case 10. *a*, Transition from sinus to atrioventricular rhythm arising in the upper levels of the atrioventricular node. *b*, Transition from atrioventricular rhythm arising in the upper part of the atrioventricular node to sinus rhythm. *c*, Taken after neosynephrin. Complexes 6 and 7 represent beats arising in the lower levels of the atrioventricular node; QRS is followed by an inverted P wave. Complex 3 is of the same type except that no P wave is visible. Complex 1 represents a beat arising in the higher levels of the atrioventricular node; the ventricular complex is anomalous. Complex 4 is transitional in form between Complex 1 and Complexes 3, 6, and 7. The remaining beats are ventricular extrasystoles. *d*, Complexes 1, 3, and 4 represent beats arising in the lower levels of the atrioventricular node; in the precordial lead (V_1), QRS is followed by an inverted P wave. Complexes 2, 5, and 6 represent ventricular extrasystoles. Complex 7 in V_1 resembles beats of questionable origin (see text), except that the QRS complex is triphasic instead of consisting of a broad, notched R. Note that the ventricular complexes of the atrioventricular beats are of the normal form.

the lead taken with the exploring electrode in the fifth intercostal space at the right sternal margin, the ventricular complex is of the same form as in the leads taken from points farther to the left. In the other leads the R component is largest in comparison with the Q deflection in those from the second intercostal space, and is either smallest or absent in those from the fifth intercostal space. In the leads from the right mid-axillary line and right anterior axillary line (level of the fourth and

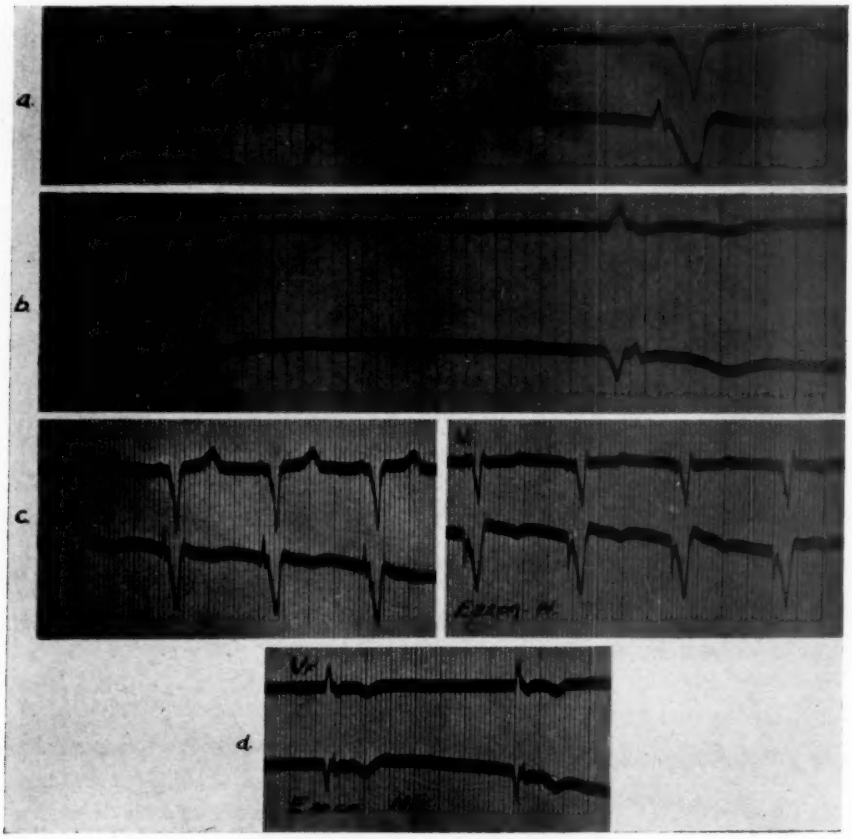

Fig. 16.—Case 10. *a*, Transition from atrioventricular rhythm arising in the upper levels of the atrioventricular node to sinus rhythm; precordial Lead V_1 taken simultaneously with a lead from the auricular level of the esophagus. *b*, Taken after neosynephrin on Jan. 7, 1944. Two beats which arose in the lower levels of the atrioventricular node (QRS followed by a P wave); lead from the auricular level of the esophagus taken simultaneously with Lead V_R. *c*, Lead from the auricular level of the esophagus taken simultaneously with precordial Lead V_1; the first strip shows sinus rhythm, the second a rhythm arising in the upper levels of the atrioventricular node. *d*, same as *b*, but with camera running at a slower speed.

fifth intercostal space), the QRS complex is represented by a QS deflection. In the leads from the left posterior axillary line and the left midscapular line (level of the fifth intercostal space), the QRS complexes are like those of the leads from the left side of the precordium. In the lead from the left paravertebral line, at the same level, QRS consists of a broad R, followed by a small S wave. In

the leads from the seventh dorsal spine and from the right paravertebral and right scapular line at the level of this spine, the QRS group is represented by a QS deflection of small voltage. Transitions from sinus to atrioventricular rhythm, or the reverse, are shown in Figs. 15, 16, 17, 18,

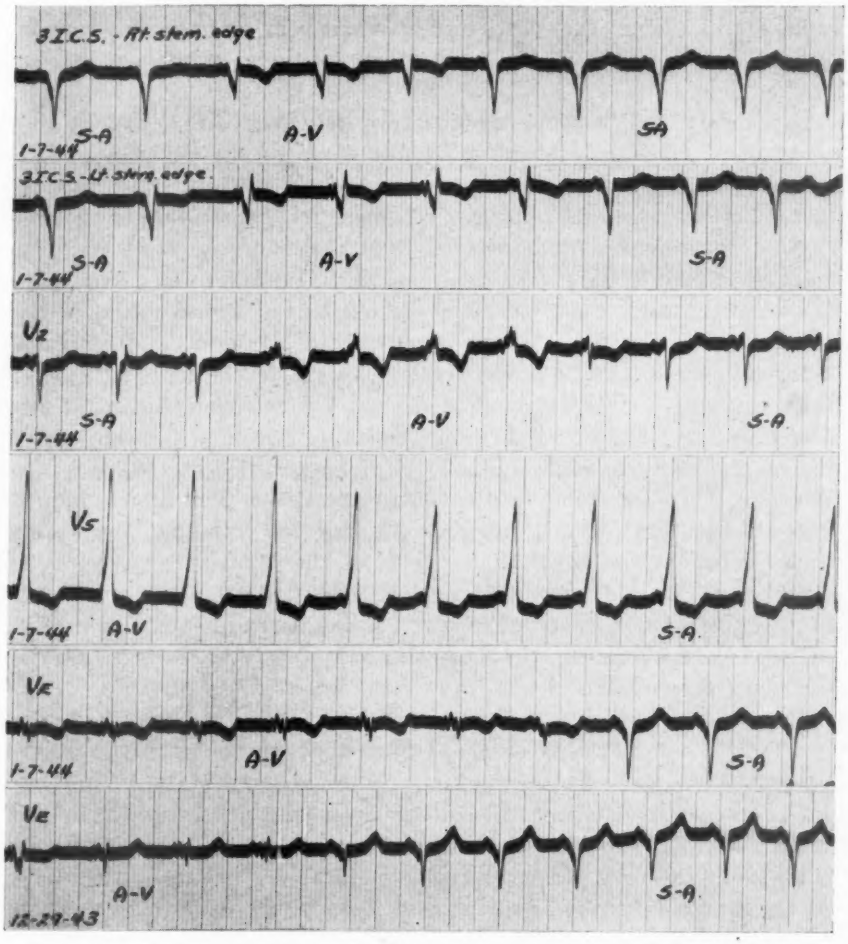

Fig. 17.—Case 10. Transitions from sinus rhythm to atrioventricular rhythm arising in the upper levels of the atrioventricular node, or vice versa. Precordial leads taken on Jan. 7, 1944.

and 19. In the limb leads (Fig. 15, *a* and *b*) the development of the ectopic rhythm was accompanied by a slight reduction in the voltage of the chief QRS deflection in Leads I and III; in the leads from the auricular levels of the esophagus it produced no noticeable change in the form of the QRS complex (Fig. 16). In Leads V_E, V_1, and V_2 (Figs. 17 and 18), however, its effect upon the character of the ventricular deflections was pronounced. It will be noted that the ventricular complexes of these leads varied in form independently of the location of the pacemaker; they were not of the same form on Jan. 11, 1944, as on Jan.

7, 1944, either when the auricular rhythm was normal or when it was ectopic (compare Fig. 18 with Fig. 17). Whether these apparently spontaneous changes in the form of the ventricular complex were produced by variations in the order of ventricular activation or by variations in the position of the heart or in the placement of the exploring electrode is uncertain. Since they have no important bearing upon the problems under consideration, we call attention to their occurrence without further comment.

It will be noted that in every instance the effect of the onset of atrioventricular rhythm upon the QRS complexes of the leads in question was to make them more like those characteristic of Group A and less like those characteristic of Group B. When the QRS complexes of the sinus rhythm were represented by broad QS deflections in leads from the margins of the sternum or in Lead V_E, they acquired a conspicuous final R deflection when the pacemaker shifted to the atrioventricular node (Fig. 17). In Lead V_2, a QRS group of the rS form became a broad, notched R wave when atrioventricular rhythm developed (Fig. 17). In the records of Fig. 18 (Leads V_E, V_1, and V_2) the change is in the same direction, although here it is more the magnitude than the character of the components that is altered. Transitions recorded at a faster camera speed are reproduced in Fig. 19. These records are particularly interesting because they demonstrate beyond question (1) that the changes under consideration involved the form of the premature component of QRS; and (2) that when the pacemaker shifted the QRS complex did not acquire its new shape abruptly, for complexes intermediate in form between those characteristic of the sinus rhythm and those characteristic of the atrioventricular rhythm are clearly depicted.

On one occasion, abrupt, but otherwise similar, changes in the contour of the QRS complex were observed while sinus rhythm was continuously present. On Jan. 7, 1944, quinidine sulfate (0.47 Gm.) was given intravenously at 12:10 P.M. During the next thirty minutes the limb leads showed a pronounced arrhythmia, an increase in heart rate, and some modification of the ventricular complexes. Changes in the location of the pacemaker were frequent, and these produced effects comparable to those already described. No changes in auricular rhythm were recorded in the chest leads taken during this period. At 12:40 P.M., however, a record of Lead V_1, taken simultaneously with Lead III, showed changes in the character of the ventricular complexes, even though sinus rhythm was continuously present (Fig. 18). At the beginning of this record the QRS group of the chest lead consists of a broad, notched R, but from time to time two or three QRS complexes in succession are represented by broad downward deflections, followed by a small R component. In later parts of the tracing the number of complexes of the second type rapidly increases, and those of the first type disappear.

On Dec. 31, 1943, and on Jan. 7, 1944, records were taken after the intravenous injection of neosynephrin (0.15 mg. on the first date and

0.12 mg. on the second). On the first occasion standard limb leads were employed. Before the drug was given, atrioventricular rhythm of the kind already described was present. The earliest effects of the drug were slowing of the heart rate, variations in the location of the pacemaker, and arrhythmia due to ventricular extrasystoles. There are

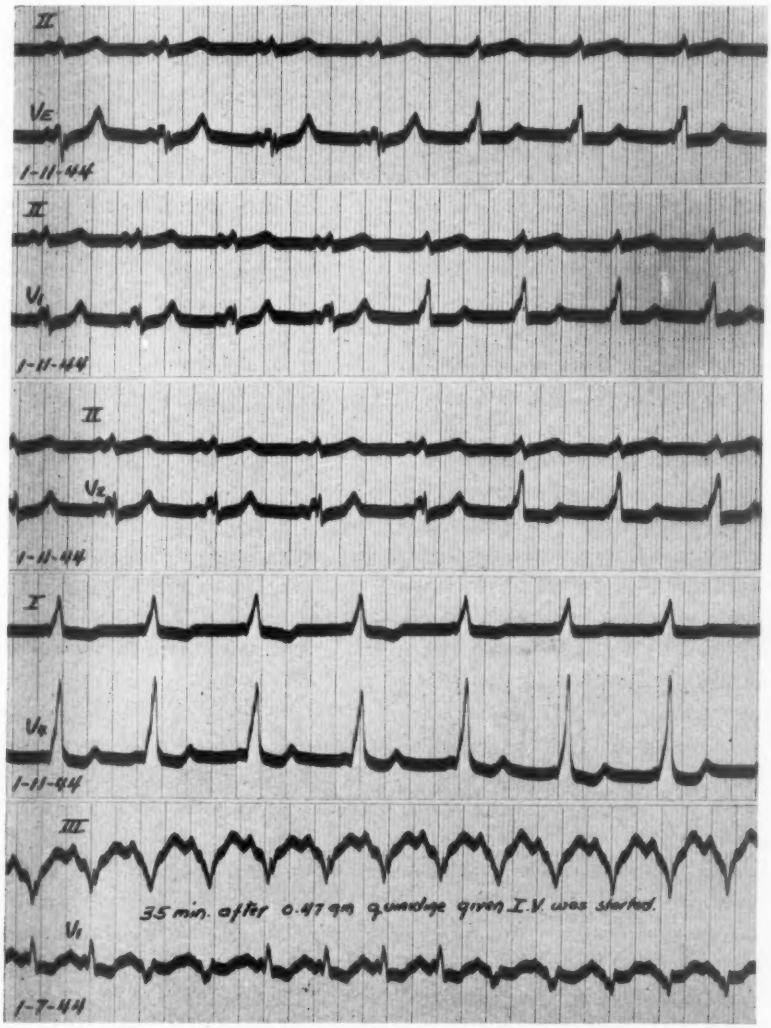

Fig. 18.—Case 10. *a*, *b*, *c*, and *d*, Transitions from sinus rhythm to atrioventricular rhythm arising in the upper levels of the atrioventricular node. Precordial leads taken simultaneously with a standard limb lead on Jan. 11, 1944. *e*, Variations in the form of the ventricular complex after the intravenous administration of quinidine when sinus rhythm was continuously present (Jan. 7, 1944).

short strips of record in which all of the beats, and others in which all of the beats other than those which are obviously ventricular extrasystoles, are represented by ventricular complexes of the normal form (Fig. 15, *c*). In the majority of instances the QRS deflections of these

beats are immediately followed by inverted P waves both in Lead II and Lead III. In other instances the initial QRS component is preceded by a conspicuous dip, which apparently represents the first limb of an inverted P wave which is partly superimposed upon the ventricular deflections. In still others no trace of a P deflection is visible. There is also one ventricular complex which is intermediate in form between those that represent anomalous, and those that represent normal, atrioventricular excitation (fourth complex, Fig. 15, *c*). The later sections of the record show short runs of extrasystoles represented by ventricular complexes of variable form, followed presently by the return of the original cardiac mechanism. On the second occasion, similar, but somewhat more complicated, changes in the cardiac mechanism followed the injection of the drug. Most of the records show Lead I and Lead V_1, taken simultaneously, but there is also a tracing of a lead from the auricular level of the esophagus, taken simultaneously with Lead V_F. At the beginning, sinus rhythm is present and the QRS complex of Lead V_1 is represented by a broad QS deflection. Some seconds later the pacemaker shifts to the upper levels of the atrioventricular node, and this complex displays a broad Q followed by a small R wave. Then extrasystoles begin to occur, and there are frequent transitions from atrioventricular rhythm to sinus rhythm and back again (Fig. 16, *a* and *c*). Presently we come to a strip of record in which two or more beats in succession are represented by ventricular complexes of the normal form, not accompanied by visible P waves. In this same strip of record there are beats which are similarly spaced, but represented by ventricular complexes of still another form. In Lead V_1 the QRS group consists of a broad, deeply notched R; the first peak of this deflection is less than half as high as the second. In Lead I the QRS complex is like that of the beats of sinus origin, but of smaller voltage, and no P wave can be made out. It may be that these beats were of ventricular origin, for, in parts of the record, they are irregularly spaced and occur in rapid succession. In other sections of the record there are beats represented by normal ventricular complexes which display, in Lead V_1, an inverted P wave immediately following the QRS complex (first, third, and fourth complexes, Fig. 15, *d*). Beats of similar origin were recorded in a lead from the auricular level of the esophagus (Fig. 16, *b* and *d*).

These observations demonstrate that the His bundle and its branches were capable of functioning, and that impulses arising in the lower levels of the atrioventricular node spread to the auricles and to the ventricles in the normal manner.

Do the observed effects of atrioventricular rhythm upon the form of the ventricular complex support our working hypothesis or are they in conflict with it? Let us examine certain implications of this hypothesis which we have not had occasion to consider heretofore. If an accessory atrioventricular bundle is present, the excitatory process may

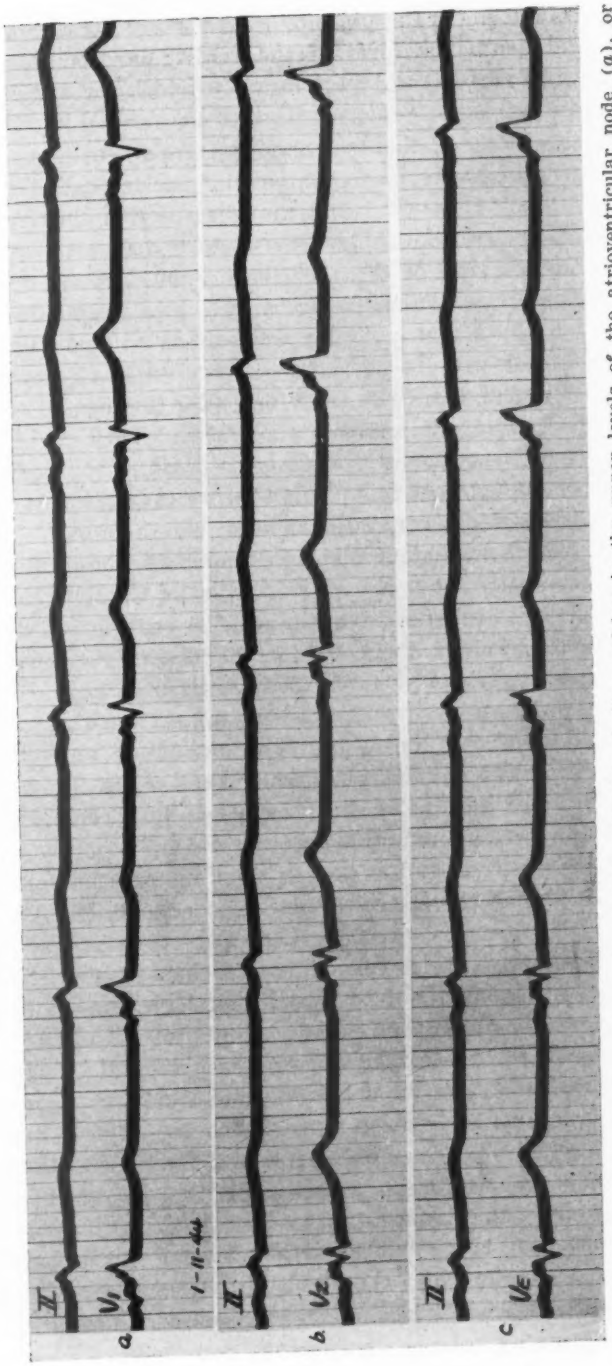

Fig. 19.—Case 10. Transitions from atrioventricular rhythm arising in the upper levels of the atrioventricular node (*a*), or vice versa (*b* and *c*), taken with the camera running at a speed of 75 mm. per second. Precordial leads taken simultaneously with Lead II. Note the transitional form of the third complex in *a* and of the corresponding complex in *c*.

spread to the ventricle both by the anomalous and by the normal route. Under these circumstances the place or places where ventricular excitation begins, and hence the form of the ventricular complex, will be determined by two factors: (1) the order in which the auricular ends of the two atrioventricular bridges pass into the excited state, and (2) the transmission times of the two atrioventricular bridges, and particularly the ratio of the transmission time of one to that of the other. The brevity of the P-R interval and the form of the ventricular complex in anomalous atrioventricular excitation requires us to suppose that the transmission time of the anomalous, is much shorter than that of the normal, pathway. In that case variations in the conductivity of either or both of the atrioventricular connections will not, unless they are very pronounced, prevent premature activation of the ventricles by the anomalous route, and will not, therefore, alter the form of the earlier fractions of the premature component of QRS. They will, however, change the relative magnitude of the anomalous and the normal components of this complex. In this connection we may mention the work of Fox, Travell, and Molofsky,[14] who showed that the administration of digitalis in a case of anomalous atrioventricular excitation may be followed by a pronounced increase in the duration of the QRS deflections, and that this effect is abolished by atropine. They attributed the alterations in the QRS brought about by these drugs to their well-known effects upon the conductivity of the atrioventricular node. We have examined the reproductions of their tracings and are not able to say with certainty that the form of the earlier fractions of the premature component either did or did not change in their experiments.

It is clear that the location of the pacemaker, by its effect upon the order of auricular activation, may determine which of the two pathways the impulse reaches first, and consequently influence the form of the ventricular complex in the same way and to the same extent as minor variations in their transmission times. Let us now assume that there are two accessory pathways, with approximately equal transmission times much shorter than that of the normal atrioventricular node and bundle. Under these conditions both the relative conductivity of these pathways and the location of the pacemaker will exert a profound influence upon the contour of the QRS complex as a whole, and also upon the form of its premature component by determining when and where ventricular excitation begins. Since active muscle is refractory to excitation, it may even happen that the excitation wave transmitted by one bundle will prevent the arrival of that transmitted by the other.

It seems to us, then, that our observations are not in conflict with the hypothesis that anomalous atrioventricular excitation depends upon the existence of one or more accessory atrioventricular bundles, if all of the implications of this hypothesis are carefully considered. We may suppose that, in Case 10, two bundles of this kind were present; that the changes in the form of the ventricular complex which accompanied the

onset of atrioventricular rhythm in this case were due to the effect of the order of auricular activation upon the time when excitation of the auricular end of each of these bundles began; and that the changes in the form of the ventricular complex which occurred independently of changes in the location of the pacemaker after the administration of quinidine were dependent upon unequal changes in the transmission times of the two pathways brought about by this drug.

It is possible that the changes in the ventricular complex that accompanied the onset of atrioventricular rhythm may be satisfactorily accounted for in another way. It is known that transitions from sinus rhythm to atrioventricular rhythm are sometimes accompanied by alterations in the ventricular complex even when the ventricles are activated in the normal manner. As far as we know, such changes are ordinarily of very small magnitude, and have been described only in connection with ectopic rhythms arising in the lower levels of the atrioventricular node. An isolated instance in which the onset of a rhythm of this sort was associated with very striking modifications of the ventricular deflections in standard limb leads has, however, been reported.[2] This phenomenon is apparently due to imperfect distribution of the excitation process to all of the fibers of the His bundle. The occurrence of reciprocal rhythm in association with a low atrioventricular pacemaker is further evidence that cross conduction in the His bundle may be limited, and that this structure and the atrioventricular node do not always function as a single, uncomplicated channel for the transmission of impulses. Nevertheless, we doubt very much whether faulty cross conduction in the His bundle played an important role in the production of the phenomenon under consideration. In the first place, it is difficult to understand why the His bundle and its subdivisions should conduct normally when the ectopic center was on the ventricular side of the junctional tissues, and abnormally when this center was in the upper part of the atrioventricular node.

The other evidence bearing upon this problem is of an indirect kind. We have pointed out that the differences between the anomalous ventricular complexes associated with the more common of the two atrioventricular rhythms observed, and those that represent responses to the sinus node are similar in character to the differences between the ventricles complexes recorded in the cases of Group A and those recorded in the cases of Group B. In both instances these differences were pronounced in the leads from the right side of the precordium, and slight in the leads from the left side of the precordium and from the auricular levels of the esophagus. It is evident that, in Case 10, they were dependent upon differences in the order of ventricular activation. We infer that the differences between Group A and Group B had a similar origin. On the other hand, there is no reason to suspect that the differences between these two groups of cases were in any way dependent upon faulty cross-conduction in the His bundle, and, consequently, it seems

unlikely that this played a part in determining the differences dependent upon the location of the pacemaker in Case 10. If these inferences are justifiable we must suppose that, in the cases of Group A, the ventricular end of the hypothetical accessory bundle was not in precisely the same location as in the cases of Group B, and, finally, that, in Case 10, there were two accessory bundles, one similar to that present in the cases of the first group and one similar to that present in the second.

PAROXYSMAL TACHYCARDIA IN ANOMALOUS ATRIOVENTRICULAR EXCITATION

Of the various types of paroxysmal rapid heart action that have been observed in cases of anomalous atrioventricular excitation, simple paroxysmal tachycardia of supraventricular origin is by far the most common. Its actual frequency is difficult to estimate, because relatively few cases of anomalous excitation in which cardiac symptoms are lacking are discovered.

Many years ago, Mines[16] produced circus contraction in rings of muscle cut from reptilian hearts in such a way as to include auricular and ventricular tissue and two atrioventricular junctions. The circulating excitation waves set up in these rings spread through the auricular and ventricular segments in succession, crossing one junction in the normal, and the other in the opposite, direction. It was suggested by the experimenter that paroxysmal tachycardia in man might be due to a similar mechanism.

The hypothesis that anomalous atrioventricular excitation is due to the presence of an accessory atrioventricular bundle has revived interest in Mines' conception of the nature of paroxysmal tachycardia. The hypothetical anomalous, and the normal, atrioventricular bundle provide the two atrioventricular junctions present in his experiments, and it has been postulated that, under proper conditions, an impulse might pass from the auricles to the ventricles by way of the atrioventricular node and bundle, and, by returning to the auricles via the anomalous bridge, initiate circus contraction. This is a plausible hypothesis, but as yet no direct evidence pointing to the existence of the postulated mechanism in an observed attack of paroxysmal tachycardia has appeared. We shall, therefore, call attention to some peculiarities of the paroxysms recorded in one of the cases of our series.

In some of the electrocardiograms taken in Case 7 there are extrasystoles represented by QRS complexes of normal outline which are immediately followed in Lead I by an inverted, and in Lead III by an upright, P wave (Fig. 20, *e*). The paroxysms of tachycardia appear to be made up of a rapid succession of beats of this type (Fig. 20, *c* and *d*). On two occasions the onset of a paroxysm was recorded (Fig. 20, *a* and *b*). In both instances the complexes of the beats of sinus origin which immediately precede the ectopic rhythm are of the anomalous type. The first ectopic beat is represented by ventricular deflections of more

normal outline, but the ventricular complexes of the first few paroxysmal beats differ considerably in form from those that follow them. The differences are of the kind usually attributed to aberrant intraventricular conduction. Since the first QRS complex of the abnormal rhythm is not preceded by a P wave, the ectopic rhythm must be ascribed to impulses arising in the lower levels of the junctional tissues. It is possible that the impulses responsible for the paroxysmal beats, as well as those that

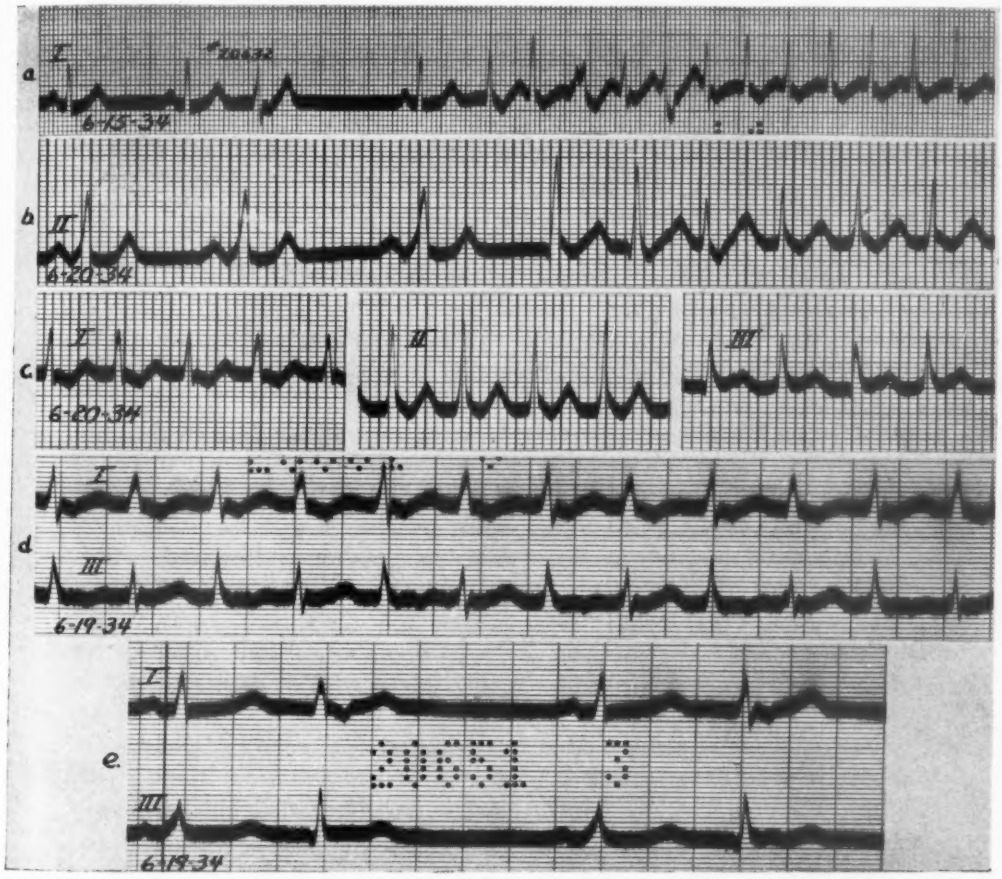

Fig. 20.—Case 7. *a* and *b*, Onset of paroxysmal tachycardia on two different occasions. *c*, Paroxysmal tachycardia on June 20, 1934; note negative P waves in Lead I and upright P waves in Lead III. *d*, Paroxysmal tachycardia on June 19, 1934. There is alternation of two types of ventricular complexes; compare with *e*, in which similar types of ventricular complexes represent extrasystoles of atrioventricular origin.

provoked the single extrasystoles, reached the auricles by the same route as in ordinary atrioventricular rhythm. The sole objection to this supposition is that it does not explain why the P waves are inverted in Lead I and upright in Lead III, and not the reverse, as is almost always, if not invariably, the case when the auricles are activated by the retrograde transmission of an impulse through the atrioventricular

node. The unusual character of the P waves led us to consider another possibility. Suppose that the path through the atrioventricular node was blocked when the ectopic impulse was liberated, and that the peculiar P waves represent auricular excitation by impulses conducted from the ventricles to the auricles via the anomalous bundle. In that case the excitatory process could return to the ventricle by the normal route, and thus initiate a paroxysm. It has been pointed out that, at the beginning of a paroxysm, there was evidence of aberrant intraventricular conduction. To explain this we may postulate that the junctional or ventricular tissues had not, as a rule, recovered completely at the time when the ectopic impulse was liberated. As a result, many extrasystoles, followed by retrograde stimulation of the auricles via the anomalous path, failed to initiate a paroxysm, and, when a paroxysm was initiated, there was aberrant conduction until the refractory period of these tissues shortened in response to the reduction in cycle length. Even during some of the longer paroxysms there was alternation of the form of the ventricular complex, indicating that intraventricular conductivity was depressed (Fig. 20, *d*). It should also be mentioned that in many instances the ventricular complexes of the single extrasystoles were not accompanied by P waves, indicating that retrograde stimulation of the auricles often failed.

We record these observations not because we consider them important evidence bearing on the problem at issue, but in the hope that those to whom the opportunity may come will make a careful study of the mechanism of the paroxysms of tachycardia that occur in cases of anomalous atrioventricular excitation from the point of view expressed. We frankly admit that the suggested interpretation of them is highly speculative, and that it does not explain the unusual P waves upon which it is based much more satisfactorily than the more conventional one.

FURTHER DISCUSSION AND CONCLUSIONS

Since anomalous atrioventricular excitation is a rare and relatively innocuous condition, it is not of major importance from the purely clinical standpoint. We do not, however, believe that this anomaly should be completely ignored by military and insurance examiners as without bearing upon the health or life expectancy of those who exhibit it. The paroxysms of tachycardia to which such persons are predisposed may certainly lead to death, and there is no reason to suppose that they may not also give rise on occasion to sudden giddiness, faintness, or syncope. In the pilot of an airplane, symptoms of this kind could result in disaster. Nor does the lack of a history of such paroxysms in the past necessarily mean that they will not occur in the future. It would seem wise, therefore, to look upon this condition as always involving such hazards as attacks of extremely rapid heart action entail.

The importance of this disorder and the interest it has aroused among cardiologists depend, however, not upon its clinical implications, but

upon its bearing on our conceptions of the mechanisms responsible for the normal sequence of auricular and ventricular contraction and the interval which separates them. We must ask ourselves whether it is possible to explain satisfactorily the electrocardiographic anomalies which characterize it without revising ideas concerning these mechanisms that seem to rest upon a solid experimental foundation. We refer particularly to the belief that in the normal mammalian heart the cardiac impulse is transmitted to the ventricles by the successive activation of the components of a specialized muscular or neuromuscular pathway, consisting of the atrioventricular node, the His bundle, and the subdivisions thereof. There is abundant experimental evidence that section of this bundle or of both its right and left branches produces complete atrioventricular dissociation. The action currents of these structures and of the node have, however, never been recorded, and there is no direct evidence available as to exactly what happens to the cardiac impulse in the latter.

We must suppose that the electrocardiographic peculiarities encountered in the syndrome under consideration depend upon an anatomic or a functional anomaly. Unless we abandon our present conceptions, any anomaly of the first sort must involve either (1) the existence of one or more muscular or neuromuscular accessory bridges extending from the auricular to the ventricular myocardium, or (2) some structural peculiarity of the atrioventricular node, bundle, or bundle branches. These two possibilities are not completely distinct, for it matters little whether the accessory channel for the transmission of impulses is widely separated from, or lies within, the same sheath as its fellow. With reference to the manner in which an accessory bundle might arise in the course of the heart's development, we may refer to observations on the junctional tissues of the embryonic mammalian heart and of the mature heart in lower orders of animals made by Keith and Flack,[17] Keith and Mackenzie,[18] Mackenzie,[19] and Mall.[20]

According to these authors, the mammalian atrioventricular bundle is derived from the invaginated portion of the auricular canal. Portions of this funnel atrophy as the lateral endocardial cushions, which form the parietal auriculoventricular valves, develop. In some fish the ring is interrupted at two points, so that the funnel is replaced by two strands. When the single ventricle of the lower forms is divided into two chambers, that part of the funnel which lies on the left side entirely disappears, so that the connection between auricular and ventricular muscle is present only on the right side. This reduction continues until, in the mammal, only the His bundle remains. In the monotreme echidna there is, in addition to an atrioventricular bundle similar to that of mammals, another leash of tissue which descends to the ventricles in the posterior angle between the parietal and septal valves on the right side. The sequence of changes by which the His bundle is de-

rived from the invaginated atrial canal was observed by Mall in human embryos.

It is logical to suppose, then, that any accessory bundle in the human heart must represent some remnant of the invaginated auricular canal. One difficulty with this supposition is that the electrocardiograms of fish, amphibians, and reptiles, and of the chick embryo display a conspicuous P-R interval[21] which, in comparison with the other intervals of the curve, is not very different from that of the normal human electrocardiogram. Why, then, should an accessory bundle derived from the invaginated auricular canal conduct the cardiac impulse with much greater speed than the normal atrioventricular bridge? Eckey and Schäfer[22] have ascribed the anomalous component of QRS in cases of the Wolff-Parkinson-White syndrome to the action currents of remnants of the original atrioventricular funnel persisting in the fully developed heart. Without considering other objections to this hypothesis, we may point out that the component in question seems much too large to be accounted for in this way.

Of the various hypotheses that have attributed anomalous atrioventricular excitation to a physiologic, rather than a structural, anomaly, the one that deserves most serious consideration is that which ascribes this disorder to the direct stimulation of ventricular fibers by the action currents of adjacent auricular muscle. Attempts to excite the ventricles to contraction in this way in experiments on animals have thus far failed, but if it should be proved possible, an anomaly of this kind would account as well as a hypothetical accessory muscular bridge for all of the phenomena observed. It should be noted, however, that observations pointing clearly to the presence of partial block in the accessory pathway would greatly strengthen the view that the anomaly is structural.

In our opinion, there has not yet been advanced any tenable hypothesis which ascribes electrocardiograms of the kind under consideration to anomalies that involve no part of the heart other than the normal junctional tissues. To be satisfactory, any hypothesis of this sort must explain the following observations relating to electrocardiograms of this type: (1) the QRS complex seems to be made up of a normal component, which begins at the normal time, and an anomalous component which begins several hundredths of a second earlier; (2) the precordial electrocardiogram is very different from the precordial electrocardiograms obtained in bundle branch block, complete or incomplete, right or left; (3) the form of the ventricular complex, including that of the premature component of QRS, is sometimes determined by the order of auricular excitation; (4) when two pacemakers, one in the sinus node and one in the upper levels of the atrioventricular node, are sending out impulses almost simultaneously, QRS complexes transitional in form between those characteristic of the sinus rhythm and those characteristic of the atrioventricular rhythm may occur. This observation implies that in one and the same cycle two supraventricular impulses may reach

the ventricles without interfering one with the other; (5) when the pacemaker shifts to the lower levels of the junctional tissues, the ventricular complex assumes the normal form. This suggests that anomalous atrioventricular excitation is impossible when ventricular excitation occurs simultaneously with, or precedes, auricular. It seems to us that any hypothesis that can satisfactorily account for these phenomena must provide more than one distinct channel for the transmission of impulses from auricles to ventricles.

CONCLUSIONS

The form of the ventricular complex in unipolar leads from the esophagus, precordium, and other parts of the thorax suggests that, in anomalous atrioventricular excitation, the dorsal wall of the ventricles is activated prematurely by impulses of supraventricular origin. There is evidence also that the normal atrioventricular node and bundle continue to function in this condition.

There are two types of cases, which differ as regards the form of the ventricular deflections in leads from the right sternal margin and adjacent parts of the right side of the thorax. The differences between these two types of cases are due, at least in part, to differences in the order of ventricular activation.

The anomalous ventricular complex assumes the normal form when the pacemaker shifts to the lower levels of the junctional tissues.

In some cases the location of the auricular pacemaker determines the form of the premature component of the QRS group, as well as that of the anomalous ventricular complex as a whole.

Our observations support the view that, in this disorder, impulses pass from the auricles to the ventricles not only by way of the atrioventricular node and His bundle, but by one or more additional channels.

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ADDENDUM

The monograph of Richard F. Öhnell, entitled *Pre-Excitation, A Cardiac Abnormality*, Stockholm, 1944, P. A. Norstedt & Söner, was not available when this article was written. In one of Öhnell's cases careful histologic examination of the atrioventricular junction disclosed an accessory atrioventricular bundle about 6 mm. long which connected the myocardium of the left auricular wall with the subepicardial myocardium of the left ventricle. This bundle was dorsal to the mitral orifice and about 4 cm. from the ventricular septum. An accessory bundle of this sort could explain the occurrence of electrocardiograms of the kind obtained in cases which we have placed in Group A.

PULMONARY ROENTGENOGRAPHIC CHANGES DUE TO MITRAL STENOSIS SIMULATING THOSE DUE TO SILICOSIS

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ROUTINE roentgenographic studies of the lungs of apparently normal persons have become increasingly widespread in recent years. Their use by the armed forces in performing screening examinations for prospective inductees is their most extensive application. Antedating this application, however, industry, with its developing awareness of the extent of the silicosis hazard, had discovered the value of periodic roentgenographic examination of the lungs of exposed men in detecting pulmonary changes due to silicosis before disability had occurred.

The value of these roentgenographic surveys is subject to certain restrictions. It has been emphasized repeatedly that a number of conditions other than silicosis cause miliary shadows in the lungs. The form and pattern of the shadows are often characteristic of a particular condition, but the definitive differential diagnosis can be made only on clinical grounds.[1, 2, 3] The following case is presented in order to emphasize the fact that the diagnosis of silicosis must be based on clinical evidence, not on roentgenographic changes alone.

CASE REPORT

The patient was a married white man, 26 years of age, who was referred to us because a diagnosis of silicosis had been made in July, 1943, by the medical examiners for the Construction Battalion of the Navy, and because the opinion had been expressed, after two subsequent roentgenologic examinations of his lungs, that the pulmonary changes were consistent with this diagnosis.

An employment survey made by Dunn and Bradstreet revealed that this man had had no hazardous dust exposure before he became a catalyst operator in April, 1943, for the company he was working for at the time of his examination in October, 1943.

By July, 1943, he had been working eighty-three days in a building in which a crusher of filter material was operated. This filter material consisted of finely ground silica, with a binder of potassium silicate. It was received in rather large pieces, which were then crushed to lumps about the size of a finger tip for use in the filters. The silica was not ground and the filter material was not prepared at this site; the only operation was the crushing. This was done in a crusher provided with exhaust ventilation, and "fines" were sifted out also under exhaust ventilation. The operation was not considered to be a dusty one. The major part of the patient's work, although carried out in the same building, was done at some distance from this crusher.

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Received for publication April 6, 1944.

The patient confirmed this history of employment. In his opinion, there was scarcely any visible dust about the crusher. Moreover, he worked at the other end of the building, upstairs, and did not operate this machine. His past history revealed that he had never been in the mines, and, as far as he knew, had never had an occupational exposure to dust. He had been under a physician's care for a sore throat for three or four days, seven years before. There had been no other illness, and no suggestion of rheumatic fever.

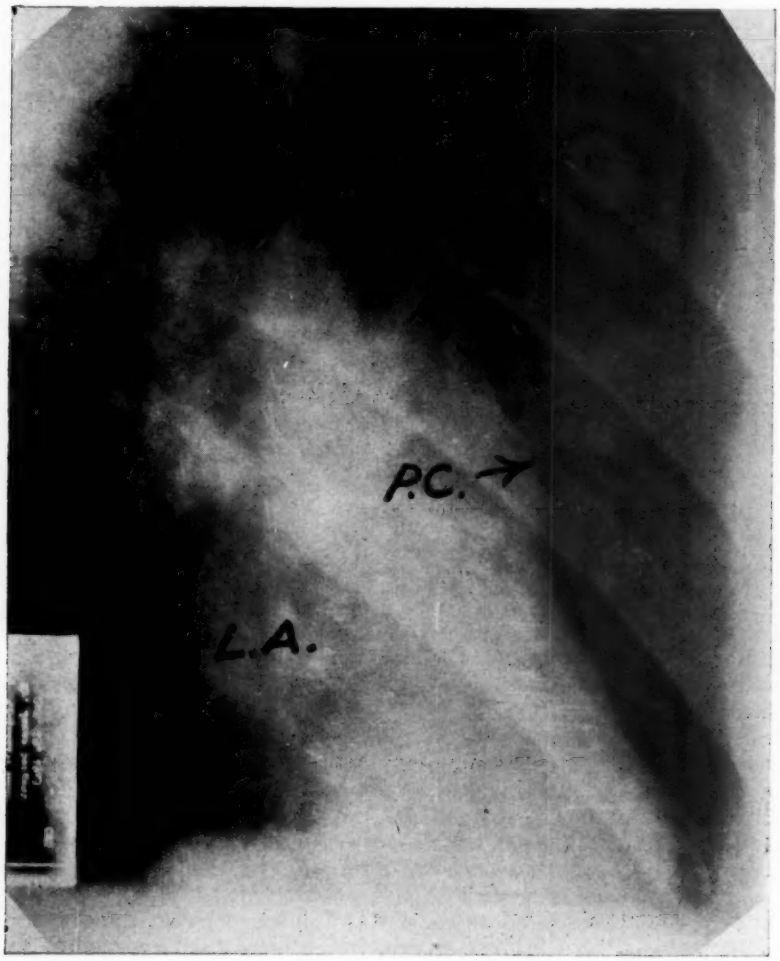

Fig. 1.—Right anterior oblique view of heart, showing prominence of the pulmonary conus (P.C.) and left atrium (L.A.).

The patient said that his usual weight was 145 pounds, dressed, and that there had been no recent change. His strength, endurance, and appetite were good. He had had no chest pain of any kind. Occasionally he had a slight cough which was productive of white sputum. In his opinion, the slight shortness of breath on exertion from which he suffered was due to lack of exercise.

Physical examination, Oct. 19, 1943, showed that the patient was a well-developed, well-nourished, slight, intelligent, cooperative, and cheerful young man who looked well. His height was 5 feet 7¾ inches; weight, 138 pounds, stripped; temperature, 98.9° F. (mouth); pulse rate, 66; respirations, 16; blood pressure, 130/75 (right arm, sitting); and vital capacity 2.95, 3.10, and 3.30 liters, standing. (The normal vital capacity for his height is 4.4 liters.)

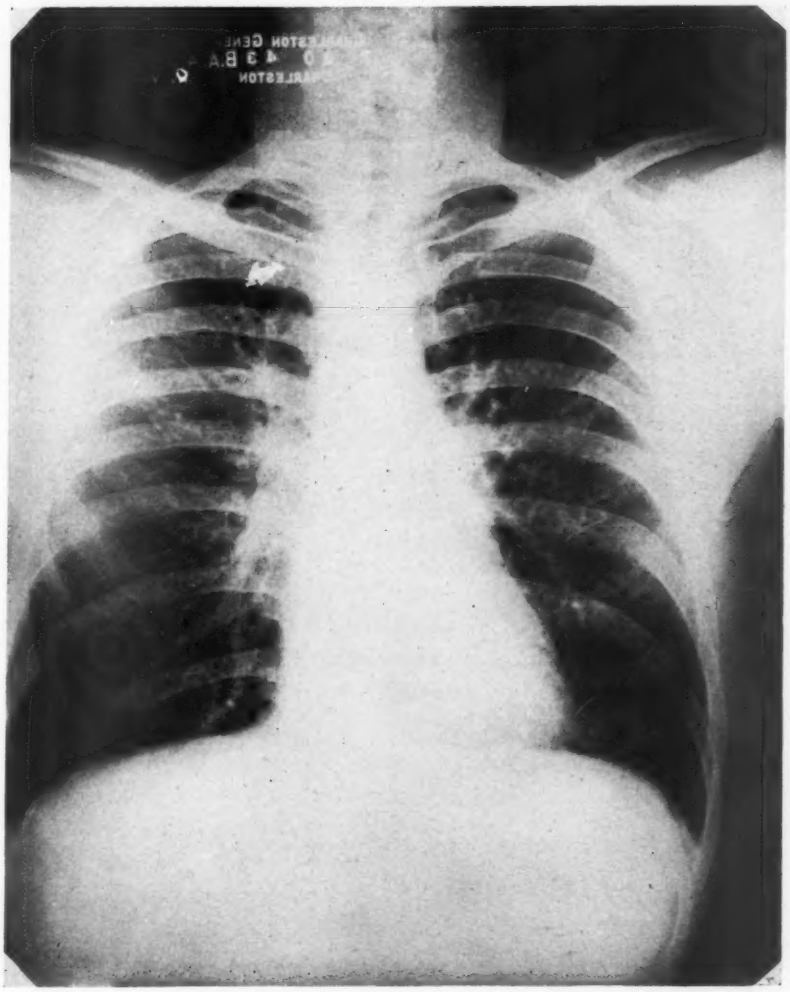

Fig. 2.—Anteroposterior view of chest, July 30, 1943.

The chest was symmetrical, with no increase in the anteroposterior diameter. The diaphragm moved well; the right side was little higher than the left. The lungs were normal anteriorly and posteriorly to percussion and auscultation. There were no changes in tactile or vocal fremitus.

The cardiac mechanism was normal. The posterior maximal cardiac impulse was in the fifth intercostal space in the left midclavicular line.

The aortic second, pulmonic second, and second heart sound at the mitral area were widely split. The first sound at the mitral area was markedly accentuated; the pulmonic second sound was sharp and accentuated. There was a rumbling, holodiastolic bruit, with presystolic accentuation, at the apex. In the absence of aortic insufficiency, this bruit is pathognomonic of mitral stenosis. No other bruits were heard before or after exercise in any position. There was no gallop rhythm, thrill, or rub.

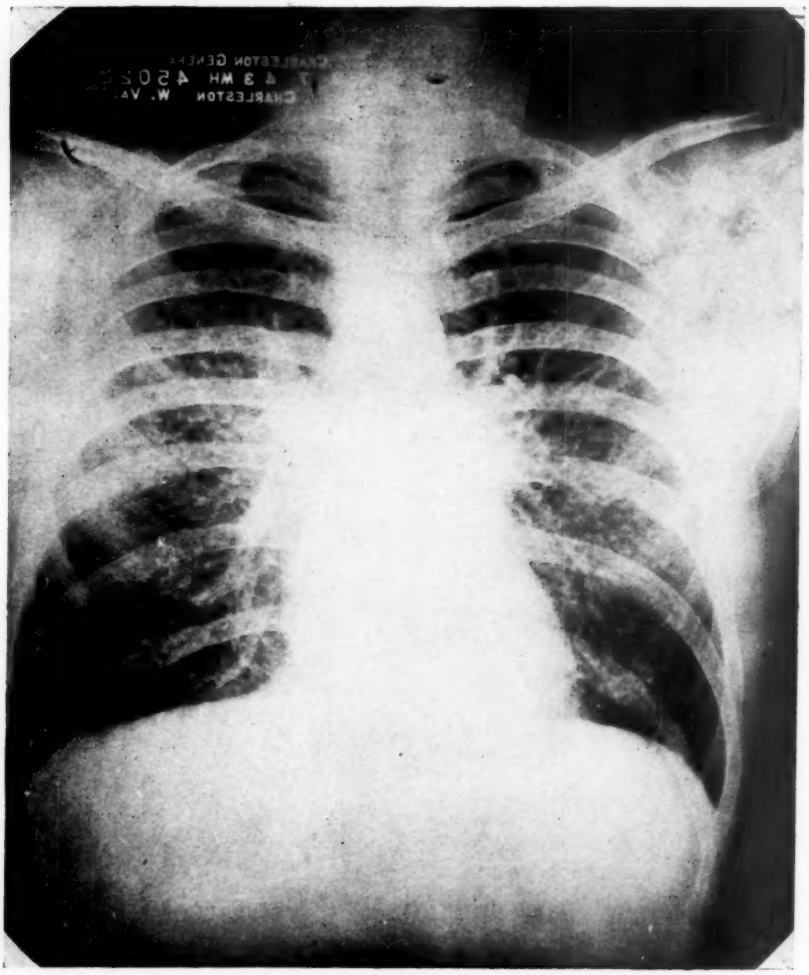

Fig. 3.—Anteroposterior view of chest, Sept. 7, 1943.

Examination of the abdomen revealed no tenderness and no masses. The liver was normal in size. The kidneys and spleen were not felt. There was no peripheral edema, no adenopathy, and no venous distention.

The urine was yellow and clear, with a specific gravity of 1.020; tests for albumin and sugar gave negative results. The centrifuged sediment showed mucus and occasional leucocytes. The hemoglobin content of the

blood was 17 Gm. (Sahli); the erythrocytes numbered 5,040,000, and the leucocytes, 8,350, per cubic millimeter; of the latter, 73.5 per cent were polymorphonuclear leucocytes, 21 per cent were lymphocytes, 5 per cent were monocytes, and 0.5 per cent were basophiles.

The patient's mean diurnal oral temperature for the seven days preceding the examination, taken by the plant physician, was 97.5 ± 0.4° F.

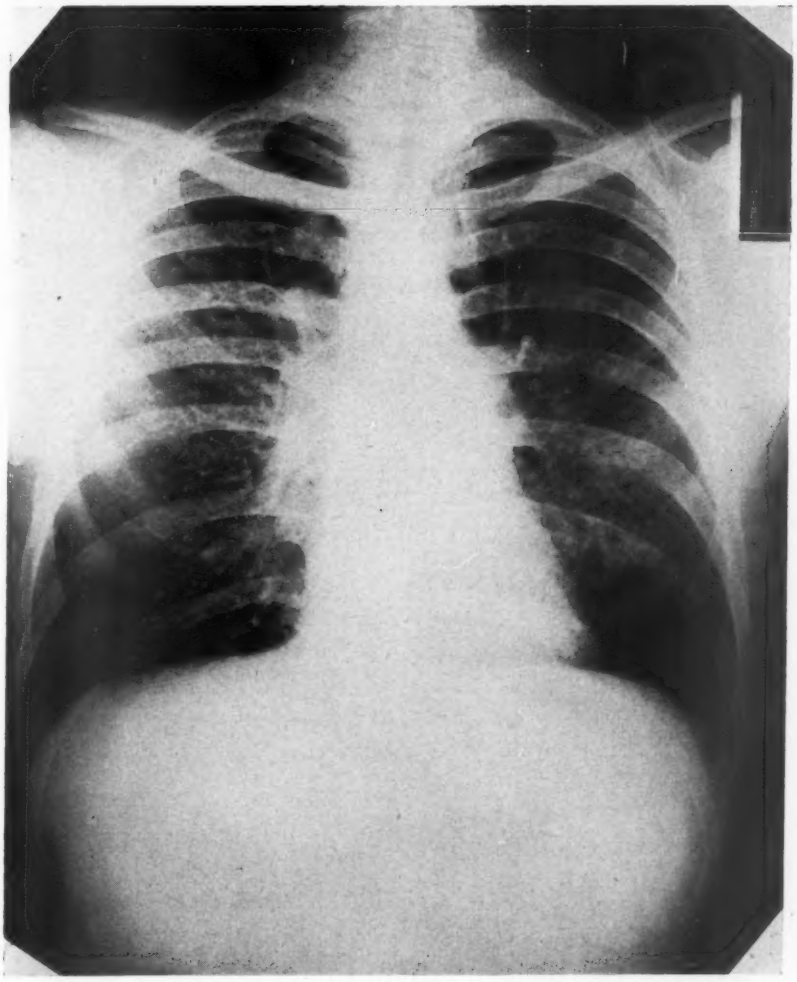

Fig. 4.—Anteroposterior view of chest, Oct. 19, 1943.

Teleostereoscopic roentgenographic examination of the chest by one of us (H. G. R.) showed that the retrosternal width was 5.5 centimeters. The greatest cardiac width was 14 cm., and the thoracic was 31.5 centimeters. The cardiac waist line was obliterated, and there were very slight accentuation of the pulmonic conus and definite accentuation of the left auricular outline. Fluoroscopic examination showed that the left auricle was definitely enlarged (Fig. 1). With barium in the esophagus, no gross displacement was noted. The heart action was normal. Throughout both lungs there was diffuse mottling. This was

heaviest in the lung areas between the hila and lateral chest walls, although some mottling was present at the apices and bases. The mottling was regarded as infiltrative, and was not nearly dense enough to be the result of scarring or fibrosis. It was felt that many of these more or less discrete-looking lesions represented points at which small bronchi crossed each other (Figs. 2, 3, 4, and 5). The pleura and diaphragm appeared normal.

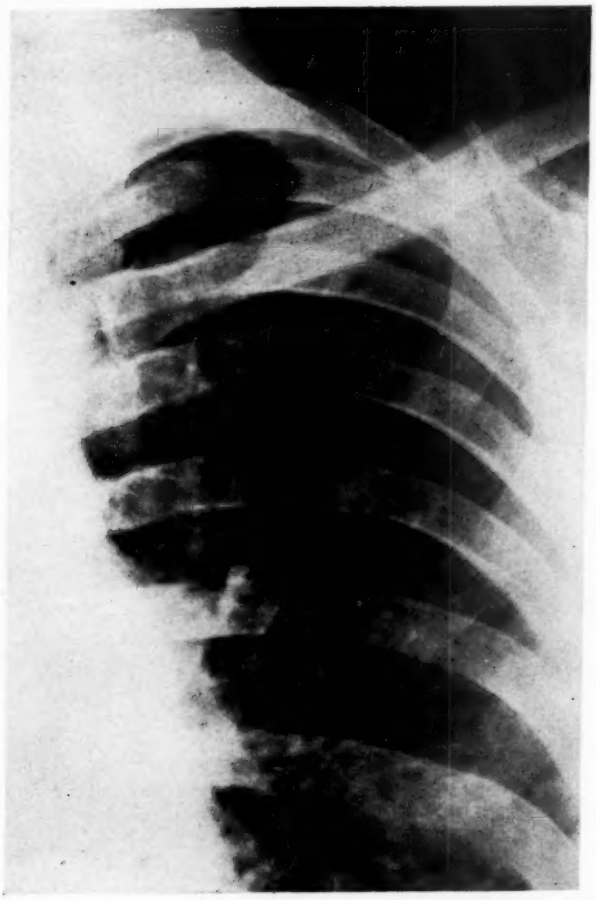

Fig. 5.—Detail of chest roentgenogram of Oct. 19, 1943, showing the soft mottling with the suggestion of nodulation. The nodulation is thickest near the hilum, and thins out toward the apex and the periphery of the lungs.

An electrocardiogram (Fig. 6) showed that the auricular and ventricular rates were 60, with slight sinus arrhythmia and sinus mechanism. The P-R interval was 0.17 second, and the QRS interval, 0.08 second. P_1 was prominent and notched, and P_2 and P_3 were prominent and slurred. There was no axis deviation. The S-T_2 and S-T_3 segments were elevated about 1 millimeter. T_2 and T_3 were upright and peaked.

The patient's employer reported that roentgenograms had been made on thirty-three of the employees who had been, and were still, working in the catalyst unit in which the patient was employed. The periods of exposure of these men varied from one to six months. In several

cases, particularly those of eight men feeding the crusher, the exposure was, in their opinion, much greater than that of the patient. Roentgenograms of these men were made and examined by a local radiologist, who, in all cases, reported nothing abnormal. We examined the roentgenograms of the eight who worked in the vicinity of the crusher and confirmed this interpretation. None of these men had developed symptoms suggestive of silicosis.

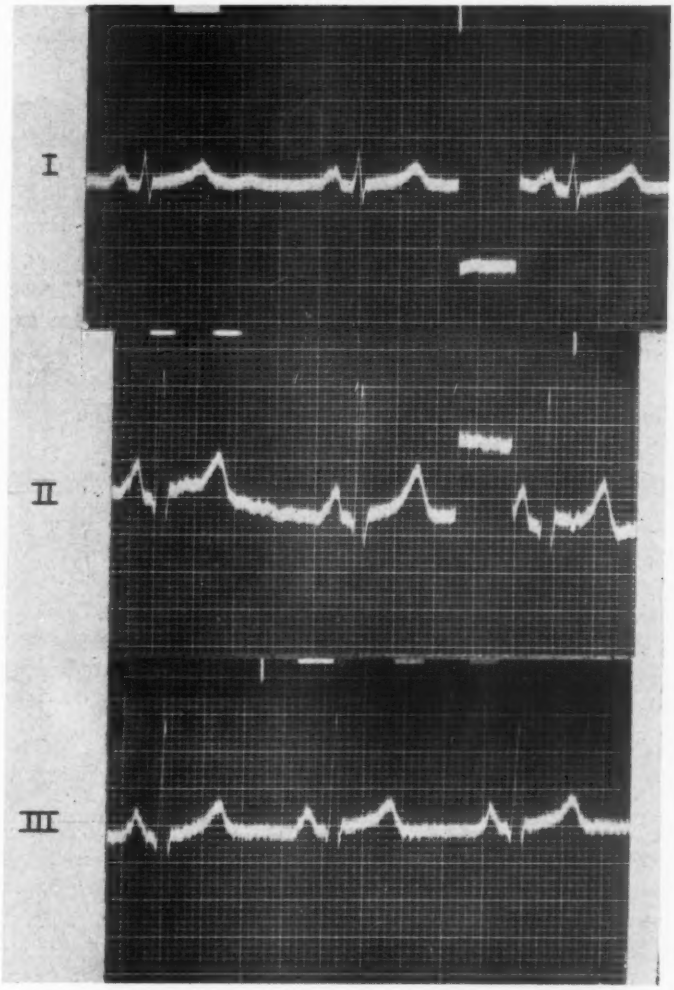

Fig. 6.—Electrocardiogram, three leads. The notched and high P waves, the elevation of the S-T_2 and S-T_3 segments, and the peaked T_2 and T_3 are found in rheumatic heart disease with mitral stenosis.

OBSERVATIONS FROM THE LITERATURE ON PULMONARY CHANGES IN MITRAL STENOSIS

Kerley[4] stated that in mitral stenosis the roentgenographic appearance of the lungs varies enormously. Occasionally, the combination of smaller end-on vessels and alveoli filled with "heart-failure cells" gives

both lungs a miliary appearance. This can be remarkably like the picture of pneumonoconiosis or miliary tuberculosis. Differentiation from these conditions is made possible, in his opinion, by the fact that, with mitral stenosis, the spots diminish toward the periphery. Attinger[5] reported that the usual pulmonary roentgenographic picture in mitral stenosis is a diffuse, even clouding in the lung bases, but that miliary lung stasis occurs occasionally, and can scarcely be distinguished from miliary tuberculosis. He stated that in miliary lung stasis the nodules are thickest in the central parts of the lungs, whereas the inferior portions, and particularly the apices, are clear. Anglin[6] reported a case of miliary stasis, with chronic passive congestion as a result of mitral stenosis, which simulated miliary tuberculosis. He stated that, although the character and distribution of the shadows suggest the correct diagnosis, they are not in themselves sufficient to distinguish between the two conditions. Roch[7] reported the case of a young woman who had been treated for tuberculosis for twelve years. There were shadows of vascular stasis in the hilar and basal regions, but the apices and costophrenic angles were clear. At autopsy she was found to have had, not tuberculosis, but mitral stenosis. Arif[8] reported the case of a miner who, after working for five years in an area where there was much silica dust, was found to have mitral stenosis, and roentgenograms of his lungs showed the finely nodular appearance of pneumonoconiosis. Arif stated that exposure in this case had been too brief to cause silicotic changes in the lungs. The patient was still alive at the time of his report.

In all these cases of mitral stenosis with roentgenographic miliary pulmonic shadows, there were symptoms of pulmonary disease, which was not true in the case here reported. Sosman[9] has noted considerable dilatation and congestion of the pulmonary vessels in cases of mitral stenosis, without any clinical signs or symptoms of illness.

OBSERVATIONS FROM THE LITERATURE ON THE OCCURRENCE OF SILICOSIS AND THE AMOUNT OF EXPOSURE REQUIRED TO PRODUCE IT

In examining a group of fiften workmen exposed in three different occupations to high concentrations of silica dust, Gardner[10] noted that all but one had developed the histologic lesions of silicosis by the time of death. Whether the exposures were as short as eight to seventeen months could not be established with certainty. In the group as a whole, roentgenographic evidence of silicosis was very slight or absent. The only changes that could readily be recognized were due to infection, although the amount of silica in the lungs was measured, and was found to equal that present in the lungs of South African gold miners with silicosis who had been exposed to silica dust for long periods. Kilgore[11] reported a study of six men who had been exposed to alkaline silica mixtures. Symptoms developed within nine, eleven, fourteen, and twenty-four months, respectively, in four of the six men who worked

in the dustiest part of the plant. Two of these men had very fine capillary fibrosis of the bronchial markings throughout both lungs, demonstrable roentgenologically; two others had extensive mottling throughout the lungs; the other two died from "myocarditis" (roentgenologic examination not made). Chapman[12] reported studies on three men exposed to a similar dust, who worked "in a very dusty atmosphere without protection." Symptoms appeared after eight, twenty-one, and twenty-nine months, respectively, of exposure. The first two men had roentgenologic evidence of silicosis, but the third, with similar symptoms, showed no evidence of silicosis on roentgenologic examination. Russell[13] noted the development of silicosis in a lens grinder who, in the course of his work, inhaled a fine quartz spray for eight months. Betts[14] noted the high mortality rate among a group of men employed in the dry grinding of quartzite. In portions of the mill the dust was so dense that it was impossible to recognize a person at a distance of a few feet, and an electric light looked like a spark. In a group of thirty men, with an average age of 30 years, the average survival period after starting work was twenty-nine months, and the average period of work was fourteen months. One man died within a year, after three months' exposure. Bloomfield and Dreessen[15] studied the incidence of silicosis in granite quarriers. The granite dust was 35 per cent quartz; 75 per cent of the particles were less than 2 μ in diameter, and 10 per cent were less than 1 micron. In a group with an average exposure to 112 to 144 million particles per cubic foot of air, no clinical or roentgenologic evidence of silicosis was found in any of thirteen men who worked less than five years, in eight of twelve who worked from five to nine years, in four of six who worked ten to nineteen years, or in one of five who worked more than twenty years. None of the men who were exposed to an average of less than 6 million particles per cubic foot had lesions, no matter how long they had worked. The Miners' Phthisis Medical Bureau Report[16] states that, in the gold mines of South Africa, where the dust is 80 per cent silica,[17] the average period of exposure before simple silicosis can be diagnosed is seven and one-half years, and the shortest period of exposure reported is two and one-half years.

Sayers, et al.,[18] reported on the incidence of anthracosilicosis among hard coal miners. Of the three hundred twenty-seven men who had worked less than fifteen years in the haulingways, where the dust contained 13 per cent silica and from 5 to 200 million particles per cubic foot of air, one developed silicosis. Rock workers worked in an atmosphere containing 35 per cent silica dust, with from 100 to 300+ million particles per cubic foot of air. None developed silicosis in less than two to three years; nine of seventy developed silicosis in less than fifteen years; twenty-five of thirty-nine in fifteen to twenty-four years, and thirty-two of thirty-five in twenty-five or more years. Sayers and Lanza[19] have concluded that the harmfulness of a given dust depends on the number of particles of free silica less than 10 μ in diameter in

the inhaled air, that most damage is probably produced by particles measuring between 1 and 3 μ, and that the development of silicosis depends on the amount of free silica in the air inhaled and the duration of exposure.

Pendergrass[2] and Twining[3] state that in making a differential diagnosis one must consider not only the miliary type of passive hyperemia and miliary tuberculosis, but also bronchiolitis, multiple pulmonary miliary abscesses, carcinomatosis, leucemic infiltration, disseminated actinomycosis, and Boeck's sarcoid.

The amount of silica excreted in the urine is no measure of the degree of pulmonary silicosis.[20] Except for examination of the lungs at necropsy, there are no further methods of establishing the diagnosis.[21]

PATHOLOGIC CHANGES IN MITRAL STENOSIS AND IN SILICOSIS

A comparison of the pathologic changes observed in the two diseases is of interest in that it suggests an explanation for the fact that the shadows cast by these fibrotic and proliferative lesions scattered throughout the lungs along the course of vessels and bronchioles are at times similar.

Gouley[22] studied the pathologic picture produced by parenchymal lung lesions in rheumatic fever and their relationship to mitral stenosis. He noted patchy interstitial fibrosis, and advanced lesions which were seen even without left auricular enlargement, particularly in mitral stenosis without mitral insufficiency. Moschcowitz[23] described the lung changes in arteriosclerosis affecting only the pulmonary circulation. This was associated with mitral stenosis in nine of his twelve cases. He stated that if the disease is of long standing, the increase in pericapillary connective tissue is so great that the alveolar wall becomes enormously thickened, and may thus give rise to a true interstitial infiltration. This thickening is due not only to the increase in connective tissue, but also to infiltration with fibroblasts. Parker and Weiss[24] described similar fibrotic changes in the lungs associated with long-standing mitral stenosis. Gloyne[25] described the nodular fibrotic changes in silicosis which are caused by minute aggregations of lymphoid tissue around the bronchioles, the branches of the pulmonary artery, the pulmonary veins, and the venous channels in the interlobar septa.

COMMENT

A case is presented in which the diagnosis of silicosis had previously been made because of abnormalities observed in repeated roentgenographic examinations.

Investigation showed that the patient had far less exposure than eight other persons who worked in the building nearer the presumed source of hazardous exposure, and that none of the others developed signs or symptoms of the disease. A search of the literature has shown that silicosis occurs only when persons are exposed to sufficiently high con-

centrations of free silica for a sufficiently long period of time, and that no cases of acute silicosis have been reported in which symptoms appeared in as brief a period as that of the patient's exposure, that is, eighty-three days. Moreover, the miliary nodulation, which was simulated by the roentgenographic changes in this case, develops only after longer exposures than those needed for the development of acute symptoms of the disease.

A picture similar to that of silicosis is found not uncommonly in roentgenographic studies of miliary tuberculosis of the lungs, and in congestive heart failure, particularly that associated with mitral valve disease. There are also rarer diseases that simulate this picture, but there is no clinical evidence that this patient suffered from any of these rarer diseases or from miliary tuberculosis.

The pathologic changes in the lungs in silicosis and mitral stenosis were mentioned to suggest a reason for the fact that the roentgenographic picture in the two diseases may at times be similar.

The patient displayed physical, electrocardiographic, and roentgenologic evidence of mitral stenosis of a degree sufficient to cause the roentgenographic changes in the lungs.

The case study emphasizes that, although routine roentgenologic examinations may be of great value in detecting asymptomatic heart and lung disease, the definitive differential diagnosis of certain of these diseases can be made only on clinical grounds.

CONCLUSIONS

Repeated roentgenographic study of the lungs may not be sufficient to establish the diagnosis of silicosis.

On the one hand, the clinical diagnosis of pulmonary silicosis can be made despite the absence of roentgenographic evidence when there is a history of adequate exposure, when pulmonary symptoms and signs characteristic of the disease are present, and when other cause for the pulmonary symptoms and signs cannot be found. On the other hand, the roentgenographic evidence may be specific.

A case is presented in which hazardous exposure to silica dust did not occur, and roentgenologic changes suggestive of pulmonary silicosis proved to be due to pulmonary congestion resulting from mitral stenosis.

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THE INCIDENCE OF HEART DISEASE IN PUERTO RICO

Statistical Analysis of 1,081 Cases

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WE HAVE already reported on the etiological types of heart disease in Puerto Rico. In 1939[1] we studied 155 cases at the Cardiac Clinic of Hospital Mimiya, 320 cases in 1941,[2] and, in 1942, while discussing a paper on "Syphilis in Puerto Rico," by Costa Mandry,[3] we gave our percentages in a series of 600 consecutive cardiovascular cases.

At present our series has reached 1,081 cases. All were native Puerto Ricans between 4 and 83 years of age; 90 per cent were white and 10 per cent were Negroes; 67 per cent were males, and 33 per cent, females. Private patients comprised 65.5 per cent of the series, and 34.5 per cent were ward patients, most of them agricultural laborers and veterans of the first World War. It was a heterogeneous group representing all economic and social strata, with a predominance of the upper, or intellectual and well-to-do, classes. Some of the patients came from distant parts of the island, but the majority were residents of San Juan or of neighboring towns.

The series included six cases of subacute bacterial endocarditis, which were classified as either rheumatic or congenital heart disease. Two cases of dextrocardia, three cases of acute bacterial endocarditis, and four cases of chronic cor pulmonale due to pulmonary schistosomiasis were not included.

All of the patients had electrocardiograms, and some had stethograms, phlebograms, and teleroentgenograms; cardiac measurements and cardiac function tests, such as the vital capacity, venous pressure, and circulation time, were also made. Either the Wassermann, Kline, or Kahn test was performed on most of the adult patients. When the diagnosis seemed evident, no laboratory data were obtained.

CLIMATOLOGY

Puerto Rico is a small, nearly rectangular island with an area of 3,400 square miles, situated between parallels of 18° and 19° north latitude. Its position with reference to the equator is approximately that of Hawaii, Jamaica, and St. Thomas. Mountain ranges, with a maximum elevation of 4,000 feet, extend obliquely across the island from the northeast to the southwest corners. They lie 25 miles to the south and 20 miles to the southeast of San Juan. Their average elevation is

Received for publication June 7, 1944.
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800 feet. The towns of Aibonito and Orocovis are 2,000 feet above sea level; Barranquitas and Adjuntas are 1,700 feet, and Lares and Maricao, 1,400 feet, but San Juan, the capital, is only 100 feet above sea level.

The climate is tropical marine, slightly modified by insular influences. The effect of land and sea breezes causes land winds at night, and, consequently, somewhat lower night temperatures. This air drainage from the high altitudes in the interior of the island to the coast results in delightful night temperatures, especially during the winter months. The mean temperature for the entire island is 73° in winter and 79° in summer, with an average temperature of 76.6°.

The average annual rainfall is 72.62 inches. It is lowest in the south, with an average of 40 inches, and highest in the west, and around Luquillo, where it is more than 80 inches. The highest readings have been recorded at the Meteorological Station of Río Blanco, with 144.99 inches, and the lowest at Santa Rita, with only 29.62 inches. There is more rain during summer and autumn and less during winter and spring.

Notwithstanding the fact that San Juan has an average of 212 days a year with rain, there is an average of only five days a year entirely without sunshine. Except for the rains that occur in connection with infrequent tropical cyclones, rainfall comes in the form of brief showers which last a few minutes and are invariably followed by sunshine. At San Juan there is an annual average of 2,847 hours of sunshine, as contrasted with 300 to 500 hours in Paris and Berlin, and 800 hours in New York. There is also a high level of solar ultraviolet radiation.

The mean barometric pressure at San Juan from 1899 to 1930 was 29.90 inches; the lowest was 29.83, and the highest, 29.95 inches. The mean relative humidity for the same period was 78 per cent at 9:00 A.M., 76 per cent at noon, and 80 per cent at 9:00 P.M. We have, therefore, a stable barometric pressure and a rather high humidity.

In the year 1915 heart disease was the seventh most important cause of death in Puerto Rico, but since 1942 it has reached fourth place. Diarrhea and enteritis occupy first place, tuberculosis, second, and pneumonia, third. It is our impression, as suggested by Fernós,[4] in 1938, that in a not distant future, as a consequence of the improvement in the public health and sanitary conditions of the island—including better nutrition—the present three most important causes of death will become secondary health problems, and heart disease will be, as in most civilized countries, the chief cause of death.

Table I shows the mortality rates per 100,000 population for the seven most important causes in Puerto Rico during 1942 and 1943.

According to De la Pila Iglesias,[5] heart disease is the cause of 23.5 per cent of all deaths in Puerto Rico, and 38 per cent of all deaths in the United States. The same author states that, in the year 1938, there were 268.9 deaths from heart disease per 100,000 population in the

TABLE I

PUERTO RICO MORTALITY STATISTICS
DEATHS PER 100,000 POPULATION

CAUSE	1942	1943
Diarrhea and enteritis	331.4	286.6
Tuberculosis	244.5	230.1
Pneumonia	141.5	121.2
Heart disease	111.9	102.4
Malaria	99.4	59.0
Nephritis	98.7	80.7
Cancer	54.8	50.1

United States, 119.8 in Puerto Rico, 113.3 in Hawaii, and 128.1 in the state of Oklahoma; the latter was the lowest figure for all the states in the Union.

In a series of 1,259 complete autopsies on native Puerto Ricans, 128 persons (10 per cent) were found to have died from cardiovascular disease, whereas large series of autopsies in the United States give a percentage average of 38 for diseases of the heart. The incidence of the various kinds of cardiovascular disease encountered in the group of 128 persons was given by Koppisch[6] as follows: syphilitic heart disease, 38 cases (30 per cent); rheumatic heart disease, 26 cases (20 per cent); arteriolosclerosis, 12 cases (9.3 per cent); arteriosclerosis, 22 cases (17 per cent); congenital lesions, 10 cases (7.8 per cent); acute bacterial endocarditis, 7 cases (5.5 per cent); subacute bacterial endocarditis, 10 cases (7.8 per cent); one case (0.7 per cent) of diphtheritic myocarditis; and one case (0.7 per cent) of hyperthyroidism. There was also one case (0.7 per cent) of chronic endocarditis of unknown cause.

Twenty (over 50 per cent) of the 38 patients with syphilitic heart disease had a complicating aortic aneurysm, and 13 (over 50 per cent) of the 22 patients with arteriosclerosis were found to have coronary occlusion or myocardial infarcts.

According to Koppisch's[6] post-mortem studies of 128 cases (Table II), syphilis is the most important cause of death (30 per cent), followed by

TABLE II

CARDIOVASCULAR DISEASE IN PUERTO RICO
ANALYSIS OF 1,259 AUTOPSIES
(Koppisch, 1944)

CAUSE	NUMBER OF CASES	%
Syphilitic heart disease	38	30.0
Rheumatic heart disease	26	20.0
Arteriolosclerosis	12	9.3
Arteriosclerosis	22	17.0
Congenital heart disease	10	7.8
Endocarditis, bacterial, acute	7	5.5
Endocarditis, bacterial, subacute	10	7.8
Myocarditis, diphtherial	1	0.7
Hyperthyroidism	1	0.7
Endocarditis, chronic, cause unknown	1	0.7
	128	

rheumatic fever (20 per cent), arteriosclerosis (17 per cent), and arteriolosclerosis or hypertension (9.3 per cent). These autopsies were made on people who belonged chiefly to the low social and economic groups of the island.

GENERAL CONSIDERATIONS

Table III gives the total number of deaths in Puerto Rico from diseases of the heart during the year 1942, as computed by the Bureau of Vital Statistics of the Insular Department of Health.

From the available mortality statistics, based on the *International List of Causes of Death*, it is impossible to distinguish the infectious from the degenerative varieties of cardiovascular disease. Cases of rheumatic carditis in people over 45 years of age have been included under list No. 92 as "Chronic Affections of the Valves of the Endocardium," and in list No. 95 with "Other Diseases of the Heart." Arteriosclerotic heart disease appears in list No. 93 with "Diseases of the Myocardium." Hypertensive cardiovascular disease does not appear in the List, and probably most of these cases were included under nephritis. The total number of deaths from all diseases of the heart in 1942 was 2,177, or 111.9 per 100,000. The death rate was lower in the rural (81 per 100,000), than in the urban, population (170.2 per 100,000) as is true in other places. At least, Table III points definitely to the fact that diseases of the myocardium, diseases of the coronary arteries, and angina pectoris—all of them of predominantly arteriosclerotic origin, degenerative types of cardiovascular disease—represent nearly 60 per cent of the total number of deaths from diseases of the heart.

According to Cossio,[7] Argentina, with a population of 13,000,000, has 260,000 cases of diseases of the heart, an average of 2 per cent. Diseases of the heart were found in 1.4 per cent of 6,806 soldiers 20 years of age, in 2.4 per cent of 10,000 school children, and in 3 per cent of railway employees whose average age was 35 years. A similar average of 2 per cent for the general population is given by Chavez[8] for Mexico, and

TABLE III

TOTAL DEATHS IN PUERTO RICO FROM DISEASES OF THE HEART
1942

INTER. LIST NO.	CAUSES OF DEATH	URBAN		RURAL		TOTAL	
		DEATHS	RATE	DEATHS	RATE	DEATHS	RATE
90	Pericarditis	4	0.6	---	---	4	0.2
91	Acute endocarditis	16	2.4	9	0.7	25	1.3
92	Chronic affection of the valves and endocardium	176	26.1	154	12.1	330	17.0
93	Diseases of the myocardium	475	70.4	498	39.2	973	50.0
94A	Diseases of the coronary arteries	159	23.6	84	6.6	243	12.5
94B	Angina pectoris	34	5.0	44	3.5	78	4.0
95	Other diseases of the heart	284	42.1	240	18.9	524	26.9
90 to 95	All diseases of the heart	1,148	170.2	1,029	81.0	2,177	111.9

by Parran[9] for the United States. In Puerto Rico we do not have similar data for comparison, except that, of 31,600 men between 18 and 38 years of age who had been carefully examined, 1.5 per cent were found to be suffering from diseases of the heart.

Rheumatism.—The prevalence of rheumatic heart disease is dependent upon many factors, among which are climate, geographical location, racial or hereditary predisposition, and living conditions.

The five most important theories are that it is caused by: (1) a specific, nonhemolytic streptococcus; (2) tissue hypersensitiveness to the streptococcus; (3) infection superimposed on vitamin "C" deficiency (Rinehart); (4) a hemolytic streptococcus (Coburn), and (5) a filtrable virus (Schlesinger, Signy, Ames, and Barnard). At present the evidence in favor of the beta-hemolytic streptococcus group "A" predominates.

In connection with this theory, it is interesting that Morales-Otero, Damin, and Pomales[10] found a smaller number (only 4 per cent) of positive throat cultures for group "A" beta-hemolytic streptococci in Puerto Rican troops than in an approximately equal number of Continental troops stationed on the island for over one year. In 28.8 per cent of the latter there were positive throat cultures. This work, and that of Pomales-Lebron and Morales-Otero[11] on rhesus monkeys, furnishes additional evidence "to support the statement that the proportion of group "A" hemolytic streptococci found in the normal throat in the tropics is lower than that obtained from a similar source in temperate regions."

It has been stated that rheumatic fever does not exist, or is rare, in the tropics. So it was thought in Puerto Rico, until Dr. Hans Smetana, formerly pathologist of the School of Tropical Medicine, found, on June 28, 1930, the first case of rheumatic fever, with Aschoff's bodies, in a 15-year-old Puerto Rican boy. It may be that the clinical manifestations of rheumatic fever are mild and indefinite in the tropics, and that the joint symptoms are either mild or absent altogether, but rheumatic heart disease is far from being rare. The work of Chavez in Mexico, of García Carrillo[12, 13] in Costa Rica, of Francisco[14] and Koppisch, and our own observations in Puerto Rico prove conclusively that the incidence of rheumatic carditis in tropical and subtropical regions is equal to, or higher than, the incidence in colder climates.

The incidence of rheumatic heart disease in our own series was 24.7 per cent in 1941, when only 320 cases had been studied, and 17.4 per cent at present, in a series of 1,081 cases (Table IV). Francisco reports 32 per cent in a group of 125 cases at the Arecibo District Charity Hospital, and Koppisch's anatomicopathologic data reveal an incidence of 20 per cent in 128 deaths from diseases of the heart. Our incidence is, therefore, about the same as that reported by Cossia in Argentina (18.2 per cent) and by Porter (13.0 per cent) in Virginia. It is lower than that reported by Chavez in Mexico City (7,000 feet above sea level)

TABLE IV

	ARGENTINE 10,000 CASES COSSIO[7] 1943 (%)	MEXICO 2,400 CASES CHAVEZ[8] 1942 (%)	NEW ENGLAND WHITE[15] 1944 (%)	NEW YORK PARDEE[16] 1941 (%)	VIRGINIA 2,607 CASES PORTER 1939-1942 (%)	LOUISIANA 2,096 CASES MUSSER[17] 1942 (%)	PUERTO RICO 1,081 CASES SUÁREZ 1937-1944 (%)
Syphilis	7.7	11.2	2.0	3.0	9.0	8.3	6.1
Rheumatic	18.2	41.0	38.0	32.0	13.0	8.2	17.4
Hypertension	23.7	13.6	28.0	36.0	36.0	57.6	22.8
Arteriosclerosis	--	28.3	--		39.0	24.1	39.9
Hypothyroid	5.8	--	--	--	--	.04	2.8
Hyperthyroid		1.4	0.2	--	--	.2	2.6
Congenital	2.4	1.8	2.0	--	2.0	.7	1.0
Avitaminosis	--	--	--	--	--	.2	.9
Functional	--	--	--	--	--	--	5.8
Miscellaneous	3.7	2.0	--	--	--	--	.7

where he found a percentage of 41, by White[15] in New England (38 per cent), and by Pardee[16] in the New York Heart Clinics (32 per cent). It is higher than that given by Musser[17] for the Louisiana Charity Hospital in New Orleans (8.2 per cent).

In evaluating our figures, we should bear in mind the fact that only 64 patients (5 per cent) in our series of 1,081 cases were between 4 and 20 years of age. A larger number of children would undoubtedly have given a higher rate of rheumatic disease (Table V).

TABLE V

AGES (YR.)	NUMBER OF CASES	PER CENT
4 to 20	64	5
21 to 50	505	47
51 to 83	512	48

Syphilis.—Table IV shows that cardio-aortic syphilis is not as frequent in Puerto Rico as we have been led to believe. In the series studied for a number of years, the incidence has varied between 10 and 5.9 per cent, and the average for the total number of cases studied is 6.1 per cent. This figure is higher than that reported for the New England States (2 per cent) and for New York (3 per cent), but it is lower than that of Argentina (7.7 per cent), Mexico (11.2 per cent), Virginia (9.0 per cent), and Louisiana (8.3 per cent). Both Francisco and Koppisch give a higher incidence for syphilitic heart disease in Puerto Rico, 12.8 per cent and 30 per cent, respectively. We should recall again that their material was obtained principally from the lowest social and economic groups of our population.

Hypertension.—The incidence of hypertension, unaccompanied by apparent arteriosclerosis or angina pectoris, is 22.8 per cent (Table IV), as compared with 23.7 per cent in Argentina, 13.6 per cent in Mexico, 28 per cent in the New England States, 32 per cent in New York, and 36 per cent in Virginia. The highest incidence of hypertension is that reported in Louisiana, 57.6 per cent.

If we add the cases of hypertension to those of arteriosclerosis, we would have an incidence of heart disease due to senile degenerative changes of about 62 per cent.

Arteriosclerosis.—The expectancy of life in Puerto Rico, as computed from abridged life tables by J. L. Janer, Statistician of the Insular Department of Health for the years 1939, 1940, and 1941, and in accordance with the Reed-Merrell method, is only 46 years from birth (45.10 for the male population and 47.29 for the female population). When the age of 5 years is reached, life expectancy rises to 52.85 years (52.1 for males and 53.8 for females). The life expectancy in the United States, in 1937, was 62.25 years, 16 years more than in Puerto Rico.

According to Morales-Otero,[18] the official census of 1940 shows that 40.6 per cent of our population is made up of children below the age of 15 years, and that people over 65 years of age make up only 3.4 per cent of the total population. The group of adults over 65 years of age is twice as high in the United States, where it reaches an average of only 6.8 per cent.

Arteriosclerosis is primarily a disease of old age, and the population of Puerto Rico is pre-eminently young. Notwithstanding this fact, the incidence of arteriosclerosis in our series was 39.9 per cent (Table IV), which is equal to that of Virginia (39 per cent) and higher than that of Mexico (28.3) and Louisiana (24.1 per cent).

The incidence of arteriosclerosis and hypertensive heart disease, as given by Francisco and Koppisch, is lower than ours. The former gives figures of 20 and 25.6 per cent, respectively; the latter's figures are 17 per cent for arteriosclerotic heart disease and 9.3 per cent for arteriolosclerosis.

There were 163 cases of coronary insufficiency (15.0 per cent) in our series of 1,081 cases. Roughly, 40 per cent of the patients with arteriosclerotic heart disease showed clinical and electrocardiographic evidence of myocardial infarction.

It is a well-known fact that, in private practice, rheumatism and syphilis are less frequent than among ward patients; on the other hand, coronary disease, including angina pectoris, is much more common among private than among hospital patients.

The cause of atherosclerosis remains unsettled. The theory of altered lipid metabolism has many advocates. Some attribute the low incidence of arteriosclerosis, angina pectoris, and coronary sclerosis among the Chinese[19] to the low intake and quality of the fat in their diet. Others have suggested that a diet in which meat predominates is an important factor in atherosclerosis. However, nutritional surveys in Argentina, the United States, and Puerto Rico do not substantiate this hypothesis. The consumption of meat is 107 kg. per capita in Argentina, where the incidence of coronary disease is only 29.6, whereas, in the United States, with a lower meat consumption (66 kg. per capita) the incidence of coronary disease is 37.7 per cent, and in Puerto Rico, where the consumption

of meat is so very low (33.4 pounds, or 15 kg., per capita), coronary disease, including angina pectoris, is not at all infrequent (15 per cent), with a death rate of 16.5 per 100,000 population. Chavez seems to favor a racial factor, which operates through a nervous mechanism, in the production of hypertension, angina pectoris, and coronary occlusion, and he bases his assertion on the low incidence of the senile degenerative changes among the Indians of Mexico. Quoting from him: "For centuries the Mexican Indian has lived a slow and unharrassed life. His manual labor may sometimes be strenuous, but he knows nothing of uneasiness and anxiety. His philosophy of life is conformist, if not fatalistic. He has a well-balanced nervous system, which protects him

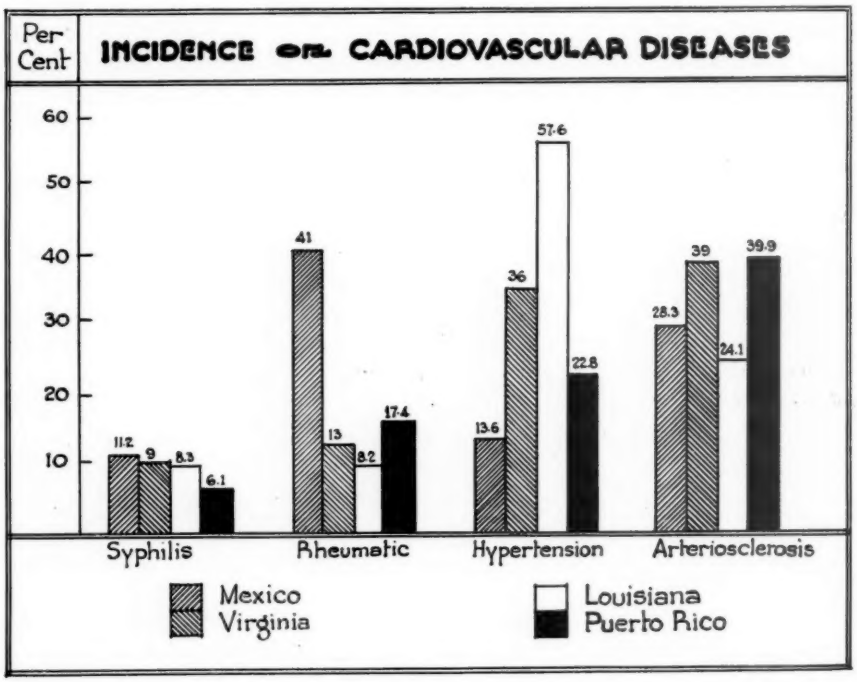

Fig. 1.

from the ordinary impacts of life, and he knows nothing of psychasthenia. What we call civilized living either does not reach him, or if it does, fails to traumatize his mind." We are inclined to believe that a similar nervous stability and a similar fatalistic philosophy of life might explain, in part, at least, the lower incidence of angina pectoris and coronary disease in our "jibaro" population (Fig. 1).

SUMMARY AND CONCLUSIONS

1. We have described the geographical position, topography, and climatology of Puerto Rico as a factor to be considered in the incidence of rheumatic fever and other diseases of the heart.

2. We have made ample use, not only of the vital statistics of the Department of Health, but also of the figures obtained and studies made by other observers in the island.

3. We have presented statistical studies based on 1,081 cardiovascular cases.

4. We have compared our own figures with those of Argentina, Mexico, the New England States, and the states of New York, Virginia, and Louisiana.

5. The incidence of the four most important etiological types of heart disease in Puerto Rico is as follows: syphilis, 6.1 per cent, rheumatic fever, 17.4 per cent, hypertension, 22.8 per cent, and arteriosclerosis, 39.9 per cent.

6. It appears from this study that climate, per se, is not a deciding factor in the prevalence of either syphilitic or rheumatic heart disease, or of heart disease due to senile degenerative changes.

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THE EFFECT OF LANATOSIDE C UPON THE PHYSIOLOGIC STATE OF ORGANICALLY DISEASED HEARTS BEFORE SYMPTOMS AND SIGNS OF HEART FAILURE APPEAR

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IT WOULD be difficult to conceive that anyone who has read a recent paper which is available to all cardiologists[1] would doubt the efficacy of the glycosides of digitalis in helping to relieve the symptoms and signs of heart failure in the presence of normal sinus rhythm. On the other hand, there is still doubt as to the value of digitalis in cases of organic heart disease in which the usual symptoms and signs of heart failure have not developed. Christian[2] felt that cardiac enlargement was retarded, and that patients with evidence of cardiac disease, but without symptoms or signs of cardiac insufficiency, were capable of greater activity without the development of symptoms of cardiac insufficiency when approximately 0.2 to 0.3 Gm. of digitalis leaves per day was administered prior to the development of symptoms and signs of heart failure. Christian's conclusions were drawn purely from his clinical observations.

Cloetta,[3] who studied the effect of digitalis on the heart of the rabbit, came to the conclusion that the dilatation and hypertrophy of rabbits' hearts with experimental aortic insufficiency never reached the same degree that occurred in the hearts of rabbits with experimental aortic insufficiency without digitalis treatment. Cloetta also was convinced from his experiments on rabbits that the absolute energy reserve of hearts with aortic insufficiency was nearly normal if digitalis was administered, whereas, if digitalis was not administered, the hearts were much more rapidly exhausted. He felt that he had proved that the capacity for work of hearts that were treated with digitalis was nearly double that of untreated hearts.

Cohn and Stewart,[4] by means of experiments on dogs in which defects in the mitral valve had been produced by operation from two to six years before the experiments were performed, found that the cardiac area, as measured roentgenologically, had increased from 5 to 94 per cent. From 25 to 30 per cent of the calculated oral lethal dose of digitalis was injected intravenously into these animals. There were a decrease in the size of the heart and a decrease in the cardiac output for the first twenty-

Partial abridgement of thesis submitted by Dr. Erickson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine. This study was aided by grants from the American Medical Association and the Sandoz Chemical Company.

Received for publication June 19, 1944.

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four hours after the intravenous injection. As the action of the digitalis began to decrease, the cardiac output returned to normal or even increased, although the heart sometimes continued to be smaller than it had been in the beginning. In our opinion, 25 to 30 per cent of the calculated oral lethal dose of digitalis, given intravenously, is a number of times the optimal digitalizing dose, and is close to a toxic dose. Kabat and Visscher[5] have shown that, when optimal doses of digitalis are applied to the tortoise heart by perfusion, there is an increase in the mechanical efficiency of the heart muscle without a change in elasticity, but when larger doses are given there is an increase in elasticity with a decrease in the work of the heart. We believe that, in the dogs' hearts studied by Cohn and Stewart, the proper therapeutic concentration of digitalis was in all probability not obtained until several days after the administration of the drug, and at this time it was noted in their experiments that, although the cardiac size was still reduced, the cardiac output was increased to the original, or greater than original, values, which indicated a favorable therapeutic response.

Stewart, Crane, Deitrick, and Thompson[6] studied the effect of giving digitalis in therapeutic doses to seventeen patients suffering from organic heart disease who had not had congestive failure. These patients had heart disease of either Type I or Type IIA, as defined in the publication entitled *Criteria for the Classification and Diagnosis of Heart Disease,* issued by the Heart Committee of the New York Tuberculosis and Health Association. These authors measured the cardiac output by the Grollman acetylene method. Roentgenograms of the cardiac silhouette were made, the cardiac area was measured, and the volume of the heart was estimated by the Bardeen formula. In their experiments, the work of the left ventricle per beat was calculated from the stroke output times the mean arterial blood pressure. These measurements were first made before digitalis was given. Then from 1.6 to 1.8 Gm. of digitalis leaves were given in twelve hours. Twenty-four to forty-eight hours after the digitalis was given, the measurements were repeated. Four of the patients showed an increase in cardiac output and a decrease in cardiac size. Seven patients showed a decrease in cardiac output as well as a decrease in cardiac size, and six patients showed no change in cardiac output or in cardiac size. The work of the left ventricle per beat was increased in every case, no matter whether the output was increased, decreased, or unaltered. If this work is interpreted in the light of Starling and Visscher's work,[7] namely, that the oxygen consumption of the heart is a function of its diastolic volume, one can state that these investigators showed that the mechanical efficiency of these compensated hearts was increased in every instance after digitalis was administered. As a result of these investigations, it would seem probable that the clinical impression of Christian, namely, that digitalis actually is of benefit when the heart is enlarged and compensated, is true.

In this paper we shall attempt to show that a glycoside of digitalis will improve the function of the heart in cases of organic heart disease in which, as yet, symptoms and signs of heart failure have not been present. We also shall compare the response of the normal heart to the same glycoside of digitalis, in an attempt to show that the function of the heart of a normal person is impaired by digitalization.

The glycoside of digitalis employed in this study was lanatoside C. We made use of this glycoside because we had used it in previous studies on cases of organic heart disease in which there were both the symptoms and signs of severe heart failure, and it had proved efficient in relieving the symptoms of heart failure in cases in which normal sinus rhythm was present. Lanatoside C is a crystalline glycoside, and its potency will always remain the same because the enzymes that destroy digitalis have been removed. There is no reason to believe that the same results would not have been obtained with other glycosides of digitalis, although there might, of course, be marked quantitative differences.

In order to obtain a clear conception of heart function and the indications for cardiac therapy, it seems essential to consider the heart as a working machine with a variable mechanical efficiency which should be maintained at the highest practicable level. The heart is a mechanical pump which converts the energy liberated by oxidation within the muscle cell into mechanical work. When the heart fails, one of two things must happen if the heart is confined in a rigid chamber which will prevent dilatation. Either the mechanical work done must decrease, and the total energy liberated by oxidation during contraction (oxygen consumption) remain the same, or the total energy liberated during contraction (oxygen consumption) must decrease, and the mechanical work decrease proportionately. The ratio of mechanical work done by a machine to the total energy liberated in the process is the mechanical efficiency, or, applied to the heart, the work of the heart divided by the oxygen consumption. Therefore, one can say that in heart failure either the mechanical efficiency decreases, in which case the work of the heart is carried out at the expense of greater oxygen consumption, or the work of the heart decreases at the same, or a greater, rate, than the oxygen consumption, in which case the mechanical efficiency remains the same or decreases. Decherd and Visscher[8] and Moe and Visscher[9] have shown that the mechanical efficiency of the heart of the experimental animal decreases in spontaneous heart failure.* Fahr and Buehler[10] have shown the same thing for the heart poisoned by cardiac poisons. Katz and Mendlowitz[11] disagreed with this conception, but the work of Moe and Visscher[9] discounted their conclusions.

Studies on the heart-lung preparation therefore indicate that myocardial failure consists, in essence, of an alteration in the energy-

*As a matter of fact, Starling and Visscher[7] showed this in their paper, but did not emphasize the fact that the decrease in mechanical efficiency was the cause of heart failure.

utilizing, and not the energy-liberating, mechanism of the heart, and that the correction of this defect should be the objective in the treatment of myocardial disease. Peters and Visscher[12] and Moe and Visscher[13] have shown that the glycosides of digitalis correct this defect by increasing the mechanical efficiency of the spontaneously failing heart, and Fahr and Buehler[10] have shown that lanatoside C does the same for hearts poisoned with cardiac toxins. Fahr and Buehler have demonstrated that, when a glycoside of digitalis (lanatoside C) improves the mechanical efficiency of a failing heart, the venous pressure on both the left and right side of the heart, which was elevated during heart failure, decreased toward the normal.

Quantitative studies of the changes in heart function and their response to digitalis can now be carried out on human hearts by the use of roentgenkymography. This actually serves as a cardiometer for the human heart, in that the systolic and diastolic volume can be measured and the stroke output can be calculated from the change in volume. In order to understand the results obtained by this technique it is necessary to elaborate a little on the experimental methods and their physiologic significance.

Starling and Visscher[7] showed that the oxygen consumption, or total energy liberation of the heart, was a function of the diastolic length of the fibers of the heart muscle. They showed that the ratio of a given change in oxygen consumption (ΔO_2) to the corresponding change in diastolic volume (ΔV_d) was a constant (throughout a very large range of change in diastolic volume), or, expressed in the form of an equation, $\frac{\Delta O_2}{\Delta V_d} = k_1$. Therefore, we can set up the equation, $O_2 = k_1 (V_d - \frac{b}{k_1})$, where O_2 is the oxygen consumption per beat, V_d is the diastolic volume of the heart at the time of the cardiac contraction which can be measured accurately in man by means of the roentgenkymograph, and b is a constant. k_1 is a constant which will differ for each heart, but has a constant value for any given heart. We can replace $\frac{b}{k_1}$ by B, and the formula for oxygen consumption becomes $O_2 = k_1 (V_d - B)$, where B is a constant which equals the volume of the undistended heart in diastole, or, in other words, when no intraventricular pressure is present during diastole. Starling and Visscher[7] proved this fundamental law of the heart on hearts which were only mildly failing spontaneously, but Fahr and Buehler[10] proved that the same holds true for hearts severely injured by cardiac poisons. We believe that this is a fundamental law of the heart; in fact, it is the real "law of the heart."

The work of any chamber of the heart per beat is the output of blood per beat times the mean blood pressure against which the blood is ejected. For this type of study, that part of the work of the heart which is represented by the kinetic energy of the blood thrown out of the heart can be neglected because it is of the order of magnitude of 3 per cent of the total. The output of the right ventricle must equal that of the left

ventricle if the circulation is to be maintained. In the heart of a normal dog, the mean pressure in the pulmonary artery is about a fourth of that in the aorta. Therefore the physiologist, in calculating the total work of the heart, usually multiplies the output of the left ventricle by the mean blood pressure in the aorta, and adds 25 per cent to this figure as a measure of the total work of the heart. The work of the human heartbeat, therefore, can be set down as $W = k_2SP$, where k_2 is a constant. S is the stroke output of the left ventricle, P is the mean blood pressure in the aorta, and W is the work of the heart per beat.

From the formula for total energy liberation and work of the heart, the mechanical efficiency with which the heart functions can be ascertained by the equation $\frac{k_2SP}{k_1(V_d - B)} = E_m$, where E_m is the mechanical efficiency. The quotient of $\frac{k_2SP}{k_1(V_d - B)}$ can be changed to $K\frac{SP}{V_d - B}$, so that the final formula for the mechanical efficiency is $E_m = K\frac{SP}{V_d - B}$, where K is a constant, S the stroke output of the left ventricle, P the mean blood pressure in the aorta, and V_d the diastolic volume. The constants K and B cannot be measured on human patients, but S, P, and V_d can. Percentage changes in the quotient $\frac{SP}{V_d}$ will always be less than percentage changes in $\frac{SP}{V_d - B}$, or the mechanical efficiency. We have called the quotient $\frac{SP}{V_d}$ the efficiency index, or E_i. It is to be emphasized that the efficiency index of a human heart is a relative, and not an absolute, expression of true mechanical efficiency. Consequently, the efficiency index cannot be used to compare the state of heart function among any group of persons; however, it will reflect accurately changes in the efficiency of the heart of a given person, and this is of primary importance in our study. We also know that the percentage changes in this efficiency index, as measured by us, are always less than the actual percentage changes in mechanical efficiency.

We measured the stroke output, S, by means of the Keys and Friedell[14, 15] method. This method is based upon changes in the frontal silhouette area of the heart, as ascertained roentgenkymographically. By this technique, the diastolic volume of the heart is ascertained very accurately through the use of a formula which relates the frontal silhouette area of the heart to the cardiac volume. Roentgenkymograms record only the changes in the frontal area of the heart that take place in the transverse diameter during systole. This systolic frontal area is then converted into the so-called systolic volume of the heart. The difference between these two volumes is a function of the true systolic output of the ventricles, and, when multiplied by a constant, gives the stroke output of the left ventricle. The stroke output of the left ventricle of fifty-four normal persons was ascertained by Keys and Friedell by the Groll-

man acetylene technique and by their roentgenkymographic method, and a very close correlation was found.

This is not the place to go into a long discussion of the relative merits of the various methods of measuring the stroke output of human hearts. One advantage of the method of Keys and Friedell over all the other methods, with perhaps the exception of the ballistocardiograph, is that it measures the regurgitant, as well as the forward flowing, components of the stroke output of the left ventricle when aortic insufficiency or mitral insufficiency is present. All of the foreign gas methods, and even the celebrated Fick method, which is usually used as a measure of the accuracy of any stroke output method, fail to measure the amount of blood that shuttles back and forth between the aorta and left ventricle in aortic insufficiency and between the left ventricle and the left auricle in mitral insufficiency. Inasmuch as many patients with heart disease will have relative or organic mitral insufficiency, and some of them will have aortic insufficiency, we believe that the method of Keys and Friedell gives a better measure of relative changes in the stroke output of the left ventricle than any foreign gas method or the Fick method. Therefore, for our purpose, which is to measure percentage changes in the efficiency of the heart, it is of no consequence whether the Keys and Friedell constants, or other constants, should be used in any given case. As long as the same technique in recording tracings and computing the silhouette area is used, the results obtained by the method of Keys and Friedell for measuring the output and volume of the heart accurately reflect changes in these functions in the same case, and reflect relative differences in these functions in a series of cases.

We measured the systolic and diastolic blood pressure by the Korotkow auscultatory method. The diastolic volume, V_d, was measured by applying the Keys and Friedell formula to the diastolic silhouette area of the heart as obtained roentgenkymographically. In any series of roentgenkymograms on the same patient, the vertical heights of the tracings were kept constant, for it is impossible to ascertain changes in this direction on the horizontal slit film with any degree of accuracy. We believe that the diastolic volume, as ascertained by this method, is very close to the actual volume of the heart, and there can be little doubt that percentage changes in diastolic volume, as obtained by this method, are accurate.

When facilities for measuring the diastolic volume and stroke output of the human heart are available, it can be shown that the mechanism of heart failure and the response to digitalis are the same as in animal experiments. Table I summarizes the data from the paper of LaDue and Fahr,[16] in which quantitative changes in the function of the heart were measured by the roentgenkymogram to ascertain the effects of lanatoside C on heart failure. The first column shows the time of observation, the second, the average venous pressure, the third, the average diastolic volume, the fourth, the average stroke output as obtained by the method

TABLE I

HEART FUNCTION IN SEVERE HEART FAILURE BEFORE AND AFTER TREATMENT

TIME OF OBSERVATION	VENOUS PRESSURE	DIASTOLIC VOLUME (V_d)	STROKE OUTPUT (S)	WORK IN KG. METER PER BEAT (SP)	EFFICIENCY INDEX (E_i)	CHANGE (%)	CASES
Effect of lanatoside C on heart failure							
Before lanatoside C	20.3	1.021	44.4	67.6	66.2	+46	10
½ to 2 hours after lanatoside C	15.0	0.980	54.0	94.7	96.6		10
Effect of lanatoside C plus rest in bed							
Before lanatoside C	19.0	0.990	42.3	72.4	73.0	+70	7
After lanatoside C and 3 to 6 weeks rest in bed	6.2	0.756	55.8	94.0	124.0		7

described, the fifth, the average work of the left ventricles, and the sixth, the average efficiency index as calculated from these data. In the seventh column we have tabulated the percentage change in the efficiency index. The number of cases studied is given in the eighth column. The percentage change in efficiency index for this part of the experiment indicates the effectiveness of lanatoside C alone. Average values are shown for seven of the cases in which investigation was carried out just before the patients were dismissed from the hospital, that is, after lanatoside C had been given and the patients had been kept on an approximate maintenance dose of lanatoside C, in addition to rest in bed and other measures used in treating heart failure, for three to six weeks. The percentage change in the efficiency index for this part of the experiment represents the results of combined treatment with lanatoside C and rest in bed. This table demonstrates that the intravenous administration of lanatoside C alone increases the efficiency index about 45 per cent within a half to two hours after administration. It also demonstrates that three to six weeks of rest in bed, in addition to the intravenous administration of lanatoside C and daily oral doses of 0.75 mg. of lanatoside C, increases the mechanical efficiency another 24 per cent. The data contained in this table show indirectly that, during the development of heart failure in these severe cases, the mechanical efficiency had decreased an average of 70 per cent. Correlated with this fall in mechanical efficiency, there was an average increase in the venous pressure of 13 cm. of water. The venous pressure decreases with treatment and the concomitant rise in mechanical efficiency.

These data prove that, in the human being, as well as in the animal, the fundamental factor in heart failure is a decrease in the percentage of the total energy liberated which is available for mechanical work during contraction, and that digitalis acts by allowing the heart to convert more of its available energy into useful work. Starr and his coworkers,[17] who studied the action of digitalis in cardiac decompensation,

also showed that when the diastolic volume was plotted against the work of the heart there was a tendency for the resultant value to move closer to the normal circulatory zone, as defined by Starr, in every instance, whether the stroke output was increased, decreased, or remained the same. Starr's method of plotting actually gives an expression which is related to changes in the mechanical efficiency of the heart under treatment, although this was not mentioned by him. The lack of agreement among investigators as to how digitalis affects the hearts of human beings with cardiac decompensation was due to the fact that the cardiac output was considered as the primary criterion of response. It is probable that both the investigators[18] who claimed that there is no increase in stroke output and those[19] who claimed that there is an increase in stroke output when decompensated hearts are digitalized were correct, and, had mechanical efficiency been calculated, they would have arrived at uniform conclusions.

The preceding studies on the mechanism of heart failure and the action of digitalis in restoring mechanical efficiency to optimal levels prompted us to study the action of digitalis on people with compensated organic heart disease. Because of the fact that cardiac enlargement is usually present in this group, it seemed probable that these hearts maintained their compensation at an increased total energy expenditure, or, in other words, functioned with a decreased mechanical efficiency. Consequently, it was conceivable that digitalis might be beneficial.

For this study we chose thirty-nine patients who had objective manifestations of organic heart disease of various types,* but who had never had evidence of congestive heart failure, such as dyspnea, orthopnea, congestion of the lungs, engorged liver, accumulation of fluid in the thoracic or abdominal cavity, or peripheral edema. The hearts varied in size from 0 to 40 per cent greater than the average normal heart, as calculated from the tables of Ungerleider and Clark.[20] All of these patients could be classified in Group 1 or Group 2A, as defined in *Criteria for the Classification and Diagnosis of Heart Disease*. These patients had normal venous pressures and circulation times. Their vital capacities were also measured, but patients with vital capacities lower than their predicted normal were not excluded if the results of other tests were normal, because this test, to a certain extent, is subjective, and the vital capacity may be changed by factors other than left ventricular failure. It is interesting that only four of these thirty-nine patients had vital capacities lower than 20 per cent of their predicted value, and in these cases there was no significant increase in vital capacity after digitalization, which would seem to show that the low vital capacities were due to factors other than passive congestion of the lung.

Circulation times were measured by injecting 3 c.c. of a 20 per cent solution of neocalglucon into the antecubital vein of the arm, held at the

*There were nine cases of rheumatic heart disease, twenty cases of hypertensive heart disease, and ten cases of coronary arteriosclerosis.

level of the right auricle with the patient in a reclining position. The test was repeated, and the average of the two readings was taken as the circulation time. As the arm-to-tongue circulation time, we used the time from the start of the injection to the time the patient announced the onset of a hot sensation in his throat.

According to Goldberg's[21] study of 156 patients, the upper limit of normal for this method is sixteen seconds. However, none of the patients with clinical evidence of heart failure had a circulation time of less than twenty seconds. Spier, Wright, and Saylor[22] said that the normal circulation time with calcium gluconate varies between seven and twenty-two seconds. Patients with circulation times up to twenty seconds were selected, provided their venous pressure was normal and no congestive râles could be heard. Seventy-five per cent of the patients had a circulation time of less than sixteen seconds; the remainder had a circulation time in the transition zone (sixteen to twenty seconds).

All observations were made between 5 and 7 P.M. The patients were instructed to eat a light lunch and to take nothing but water by mouth until they reported for the roentgenkymographic studies. The patient was placed in front of the roentgenkymograph in a standing position, and was allowed to rest in this position until the pulse rate became stabilized for five minutes. During this time the patient's blood pressure was recorded. The patient was then instructed to breathe moderately deeply and was ordered to stop breathing during the phase of mid-inspiration. While the patient held his breath, a roentgenographic exposure of two and one-fourth seconds was made with the tube target at a distance of 36 inches (91.4 cm.) from the film. The blood pressure was again measured, and, with the patient in the same position, a duplicate roentgenkymogram was made within five minutes of the original one. The roentgenkymograph was fitted with an electric timer, and the pulse rates were calculated directly from the roentgenkymogram.

Moderate inspiration was selected as the standard condition for kymographic estimation of cardiac function because the best visualization without alteration of the stroke output was attained. Keys and Friedell[14, 15] found that it is unnecessary to maintain extreme constancy in respiratory conditions, for a considerable latitude in the respiratory phase has relatively little effect on the heart volume and the stroke output as calculated by their method. It is essential to guard only against abnormally high or low intrathoracic pressures, such as occur with forced inspiration or expiration.

The response to exercise of the patients whose ability to exercise was not limited by anginal distress was then measured. The exercise consisted of ascending and descending a three-step platform with a total rise from the ground of 2½ feet (76.2 cm.) a calculated number of times in a given period of time. The amount of work to be performed was determined from tables constructed by Master and Oppenheimer,[23] which give the foot-pounds of work per minute that a normal person of stated weight, age, and sex can perform with a return of pulse rate

and blood pressure to normal pre-exercise levels within two minutes after the exercise has been completed. The patient was instructed to walk over the platform so that the calculated number of ascents was completed in one minute. One minute after completion of the exercise, roentgenkymograms were made. Blood pressure readings were taken before and after the roentgenkymograms were made. This is a rather crude test for exercise tolerance, but it served the purpose of pointing out trends in the circulatory function of the normal and compensated heart before and after the administration of digitalis.

Upon completion of these preliminary studies, the patients were given lanatoside C and instructed to take six 0.5 mg.* tablets daily for two days, and then to take one and two tablets on alternate days as a maintenance dose. They were given no further instructions and in no way were cautioned to change or restrict their activities. The patients returned one week and three weeks after the preliminary observations and the beginning of digitalization. At each of these visits the patient reported at the same time and under similar conditions as on the original visit. The same routine was followed; duplicate kymograms were made at rest, and one kymogram was made after exercise. Between the second and third observations, electrocardiograms were made in all cases and compared with the original tracings to ascertain the effect of digitalis. Eighty per cent of the subjects with abnormal hearts and 65 per cent of those with normal hearts showed electrocardiographic evidence of digitalization. At the completion of the third observation, the venous pressure, vital capacity, and circulation time were rechecked and compared with the values obtained before digitalization.

Similar procedures and observations were carried out on the fourteen normal subjects. However, only two series of observations were made because it seemed inadvisable to maintain these persons on digitalizing doses for longer periods of time. The second series of observations was made one week after digitalization, and in exactly the same manner and under the same conditions as in the group with organic heart disease.

The administration of lanatoside C was discontinued at the completion of these observations, and the patients with compensated heart disease were followed in the cardiac clinic at the Minneapolis General Hospital. Approximately six months after the administration of lanatoside C had been discontinued, eighteen of the patients were recalled and roentgenkymographic studies of their heart function were repeated, using the same routine and technique as employed in the original studies. At this time only one series of duplicate observations was made, and the patients were given no digitalis. The purpose in re-examining these patients was to confirm or invalidate the observations made on the patients with compensated heart disease when they were digitalized.

Before presenting the results of our observations, it is necessary to show some measure of the inherent variability in the method. In all our studies, duplicate roentgenkymograms, from which the calculations

*A few small, asthenic patients were given five 0.5 mg. tablets, instead of six.

of heart function were made, were taken within five minutes of each other. In Fig. 1, the scatter of duplicate values for the efficiency index is plotted. The points fall about the 45 degree line at random, and the extreme limits of variation are 18 units. Approximately as many points fall above as below the 45 degree line, and since the average of duplicate measurements was taken as the value for the efficiency index, the extremes of variation were reduced by $\frac{1}{\sqrt{2}}$, or to 12.6 units.

In Fig. 2, this zone of variability in method is plotted as a percentage variation to conform with the method of recording the results in percentage changes from the original values. This zone includes the extremes of variation in about 130 measurements. Values falling outside the zone indicate a positive or negative change from their original state, whereas values falling within the zone cannot be considered to indicate a significant change from the original values. It is apparent that a more exact statistical analysis was not necessary, for the results are clear cut.

For the purpose of constructing a graph to demonstrate the relative individual and mean change in the efficiency index, we selected that efficiency index which had the largest value, whether it occurred in the first or the third week of digitalization. We believe that this is justified, for the maximal response to therapy should occur with the best digitalizing level. Since average doses of lanatoside C had to be used for all the subjects because there was no objective way of ascertaining the optimal dose for any one person, and since there are undoubtedly variations in the optimal requirements for digitalis from person to person, one is not justified in setting either the first or the third week as the time of best degree of digitalization for all patients, or in assuming that the degree of digitalization will be the same in the first week as in the third week. Furthermore, there was no way of telling whether the patients actually followed instructions regarding dosage, because they were all ambulatory and were not seen between measurements. It is to be emphasized, however, that had the results of either the first or the third week's observations been uniformly recorded, the conclusions, as well as the magnitude and the direction of changes, would not have been altered in any significant way.

Fig. 2 shows the scatter of the relative individual and mean changes in the efficiency index from the original values, represented by the 0 per cent line in each case, when patients with compensated heart disease and when normal persons were digitalized as described. It will be noted that the efficiency index in only five of the thirty-nine cases (10 per cent) did not show an increase after digitalization. These five observations fell within the zone of variability of the method. The efficiency index of the fourteen normal hearts decreased. Analysis of this figure would seem to justify the statement that lanatoside C will increase the mechanical efficiency of the hearts of most patients with organic heart disease that are not as yet demonstrably decompensated, whereas it will de-

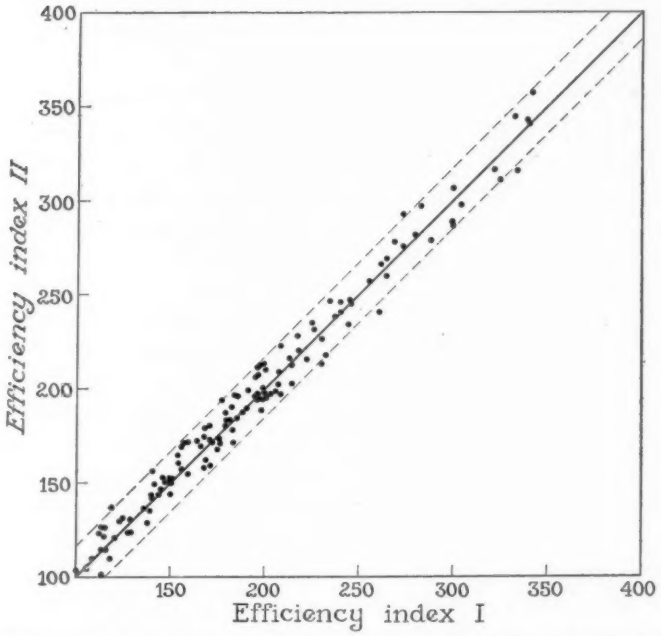

Fig. 1.—Scattergraph demonstrating the variation in duplicate measurements of the efficiency index when efficiency index I is plotted against efficiency index II.

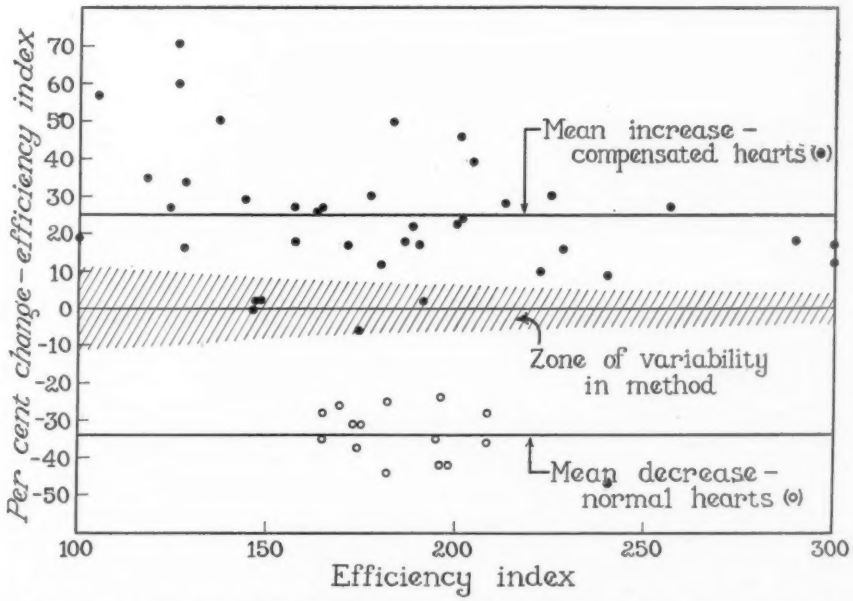

Fig. 2.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values (represented by 0 per cent line in each individual) when normal subjects and patients with compensated heart disease were digitalized.

crease the mechanical efficiency of a normal heart. In other words, glycosides of digitalis are toxic for normal hearts but are beneficial to most abnormal hearts.

It is necessary to say a few words about the five cases in which there was no increase in the efficiency index, but in which the change in efficiency index lay within the zone of variability of the method. The one patient who had a decrease of 5 per cent was thirty-six years of age, and had a blood pressure of 140/90, and a 13 per cent enlargement of the transverse diameter of his heart. He was included in this series because he had a history of anginal distress. The results of physical examination were negative and the electrocardiogram was normal. As the patient was followed, it was found that his so-called anginal distress was associated with attacks of ventricular paroxysmal tachycardia. The degree of organic heart disease was in all probability minimal, so that one might expect him to respond more like the patients with normal hearts. Of the four other patients, one was a young man, 21 years old, with a recently discovered aortic stenosis and insufficiency which were asymptomatic. The other three patients had been coming to the out-patient department of the hospital for a long time. One had coronary arteriosclerosis, another had rheumatic heart disease, and the third had hypertensive heart disease. Electrocardiograms of these patients showed no digitalis effect. Whether this means that they did not take the digitalis as directed, it is not possible to know. It is also noteworthy that all five of these patients had circulation times that were less than sixteen seconds.

The wide scatter of improvement in the efficiency index in the thirty-four cases was probably associated with varying gradations of myocardial insufficiency in this group, as yet not severe enough to produce frank symptoms and signs of cardiac failure. The normal hearts responded to digitalization with a mean decrease in efficiency of 33 per cent. The normal hearts were closely grouped, probably because the function of each heart was very similar to that of every other, and therefore the action of digitalis could be expected to produce similar results.

Fig. 3 shows the response of normal and abnormal hearts to the graded exercise tests. Before digitalization both the normal and abnormal hearts responded with an increase in the efficiency index of between 5 and 6 per cent. This observation on the human heart is in accord with the laboratory observations of Starling and Visscher,[7] who noted that the heart of the dog responded with a slight increase in mechanical efficiency when an increased load was placed on it. After digitalization, twenty-two patients with abnormal hearts responded to exercise with a mean increase in efficiency index of 29 per cent above the resting level, or 23 per cent above the efficiency index before the administration of digitalis. The normal group, on the other hand, showed a mean decrease in efficiency index of 25 per cent below the original resting values, or 30 per cent below the efficiency index before the administration of digitalis. We can therefore say that the response of compensated and

organically diseased hearts to increased strain is definitely improved by digitalis, whereas the response of normal hearts is definitely impaired by digitalis.

The change in the efficiency index caused by digitalis was of approximately the same magnitude in this series as at rest, namely, +23 per cent and –30 per cent, respectively, for abnormal and normal hearts, as contrasted with +24 per cent and –33 per cent, respectively, at rest. This degree of correlation in the magnitude and direction of response of normal and abnormal hearts to digitalis under both conditions of rest and exercise seems striking.

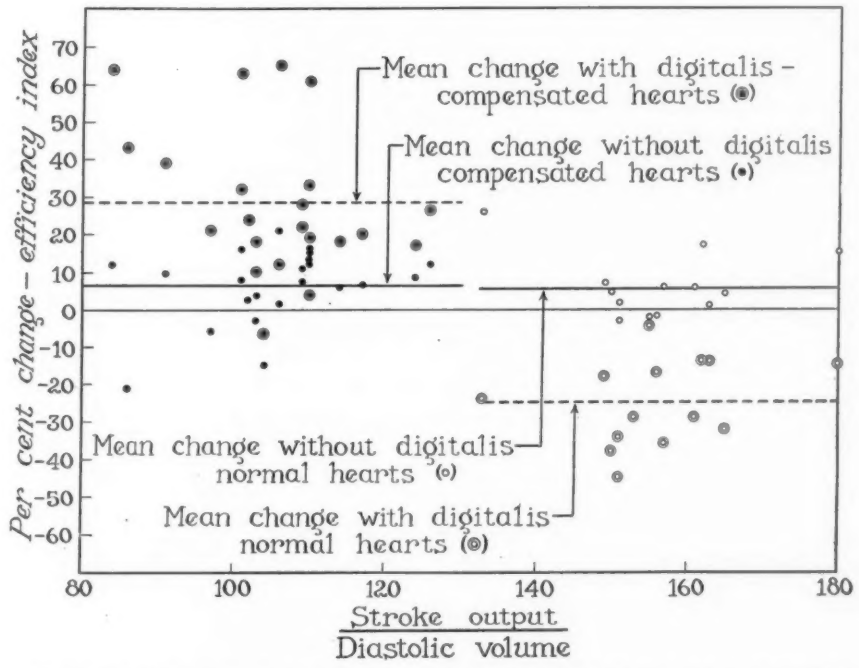

Fig. 3.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values in normal subjects and in cases of compensated heart disease caused by exercise, before digitalization and after digitalization. The changes in efficiency index are plotted against the ratio of $\frac{\text{stroke output}}{\text{diastolic volume}}$ which is a rough index of heart fitness.

Measurements of cardiac function were again made six months after the administration of digitalis had been discontinued. Fig. 4 shows the results in the eighteen cases that were restudied. Whereas the mean percentage increase in the efficiency index was 32 per cent for this group when digitalized, the mean percentage change in efficiency index was –7 per cent six months after the administration of digitalis had been discontinued. From these studies it is apparent that these patients were no better off six months after the administration of digitalis had been discontinued than they were before it was started. In nine cases (50 per cent) the function of the heart was definitely worse, as indicated

by the decrease in the efficiency index below the zone of variability of the method.

The degree of improvement in the efficiency index of the abnormal hearts was found to bear no direct relation to the size of the heart. The increase in efficiency index seemed to bear very little relationship to the type of heart disease. The mean increase in efficiency index was as follows: 22 per cent in the cases of hypertensive heart disease, 26 per cent in the cases of rheumatic heart disease, and 27 per cent in the cases of coronary arteriosclerosis. These differences in response among the types of heart disease are not significant, although there seems to be a tendency toward greatest benefit in the cases of coronary arteriosclerosis. We frequently have noticed that digitalis seems to be especially efficient in cases in which heart failure is associated with coronary arteriosclerosis. It is the limitation in oxygen supply which ultimately brings about failure in this group of cases, and it seems probable that digitalis would produce the most favorable results in this group by causing more efficient utilization of the available supply of oxygen.

There is a rough correlation between the ratio of stroke output to diastolic volume and the response to digitalis, so that the more disproportionate the stroke output to the diastolic volume, the better the response to digitalis. Likewise, this ratio segregates the normal from the abnormal heart (Fig. 3). Consequently, the ratio is valuable as a rough index of cardiac fitness, and one can say that the more disproportionate the stroke output to the diastolic volume, the less effective is the heart as a pump.

The mean change in efficiency index in the twelve cases in which the circulation time was between sixteen and twenty seconds was 39.9 per cent, whereas the mean change in efficiency index in twenty-six cases in which the circulation time was less than sixteen seconds was only 18.3 per cent. Seven of the eight patients who had an increase in their efficiency index of 35 per cent, or more, had a circulation time of between sixteen and twenty seconds. All five of the patients who fell within the zone of variability, and, consequently, showed no significant response to digitalis, belonged in the group with circulation times of less than sixteen seconds. This would seem to indicate that an increase in the circulation time appears rather early in the development of heart failure. It also would seem to indicate that one may expect a good increase in the mechanical efficiency of organically diseased hearts if digitalis is given, despite the absence of the usual signs and symptoms of frank heart failure, providing the circulation time is between sixteen and twenty seconds.

Since the efficiency index is an expression of work per beat divided by the diastolic volume, and since the work per beat is obtained by multiplying the stroke output by the mean arterial pressure, it is obvious that any one of these functions, considered by itself, is insufficient to explain the whole story of the function of the heart and its response to digitalis therapy. In Fig. 5 we have plotted the scatter of relative individual

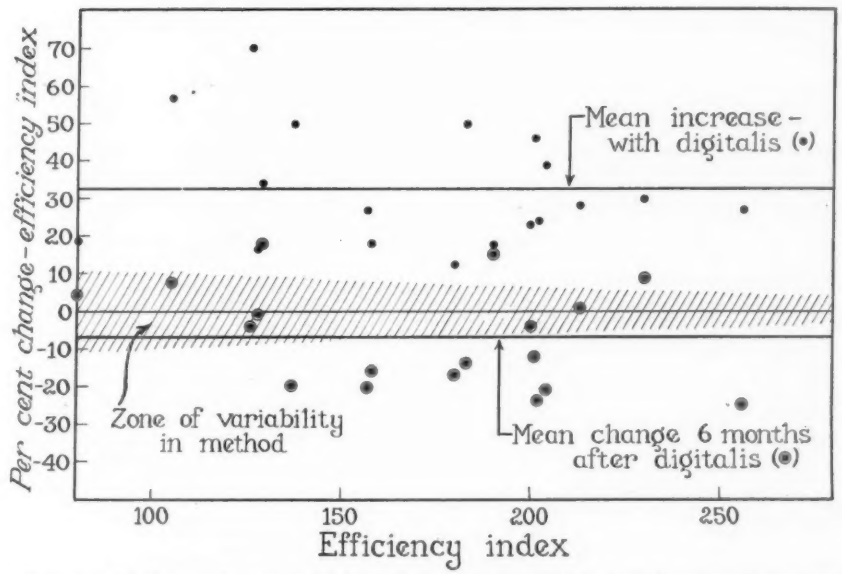

Fig. 4.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values in cases of compensated heart disease during period of digitalization and six months after administration of digitalis had been discontinued.

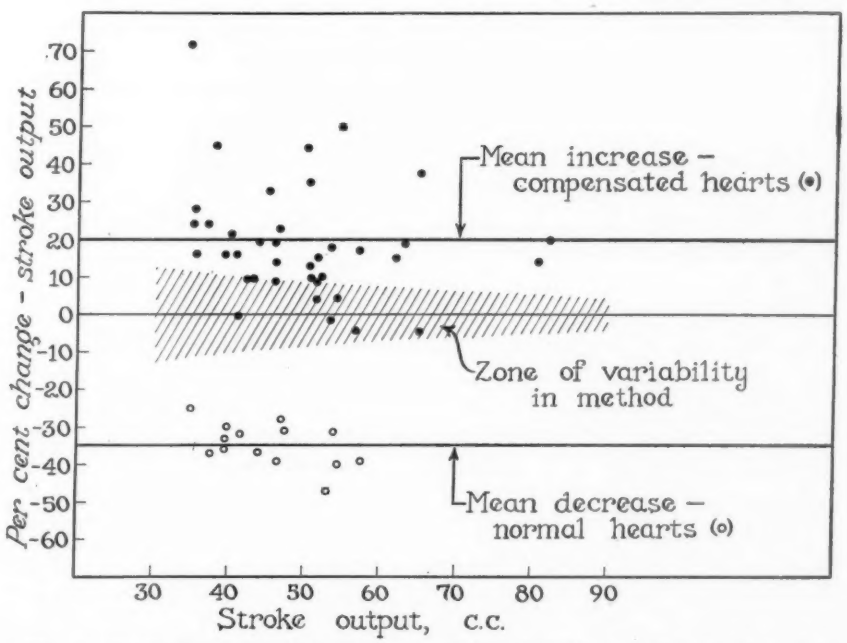

Fig. 5.—Scattergraph demonstrating the relative individual and mean change in stroke output from original values when normal subjects and patients with compensated heart disease were digitalized.

and mean changes in stroke output from original values, represented by the 0 per cent line, when patients with compensated heart disease, and when normal persons, were digitalized. The abscissas represent the original values, and the ordinates represent the percentage change in stroke output after digitalization. As in the case of the efficiency index, the maximal variation in the method of measuring the stroke output was ascertained by making a scattergraph of duplicate measurements of stroke output. All of the points are closely grouped about the 45 degree line, and have a maximal variation of 4.1 units. The zone of maximal variation in the method has been drawn in Fig. 5 as a percentage variation, to conform with the method of reporting changes in stroke output. Again a sharp difference between the response of the compensated hearts and that of the normal hearts is demonstrated. There was a mean increase of 19.4 per cent in the stroke output of the compensated hearts, whereas the normal hearts showed a mean decrease of 34.6 per cent. Twenty-nine (75 per cent) of the patients with compensated heart disease fell above the zone of variability in the method, and showed a definite increase in stroke output. The remaining ten patients (25 per cent) showed no significant change in stroke output. All of the normal subjects fell below the zone of variability in the method, and showed a significant decrease in stroke output. These observations are in accord with those of Stewart and his co-workers,[6] in that not all patients with compensated heart disease respond to digitalis with an increase in stroke output; some show no significant change. One must remember that changes in the stroke output cannot be relied on to give a complete picture of functional change in the heart after digitalization. It is necessary to know the change in blood pressure, because this is one of the factors in mechanical work, as well as the change in diastolic volume, which is a measure of total energy metabolism.

It will be noted that the original stroke output in the cases of compensated heart disease was of the same order as the original stroke output in the normal group, and it may seem perplexing that there was a marked increase in stroke output after digitalization. However, it is to be remembered that the stroke output in this compensated group was small compared with the size of the heart. In consequence of the increased diastolic volume, these compensated hearts developed more total energy per stroke than normal hearts; therefore, when enlarged hearts increase their mechanical efficiency, they will expel much more blood per beat than the normal heart if the diastolic volume remains approximately the same. Digitalis, by increasing the mechanical efficiency of these organically diseased hearts, converts more of the available energy to useful work, and if the diastolic volume remains larger than normal, it will produce an increase in stroke output. The decrease in the stroke output of the normal hearts is in accord with observations of other investigators, who noted a decrease in the stroke output of normal hearts[6, 17, 24, 25] of human beings and dogs when digitalis was given.[26-28]

Both the normal and abnormal hearts showed a decrease in the diastolic volume when digitalized; the mean percentage decrease was 3.2 per cent in the normal group and 3.8 per cent in the abnormal group,

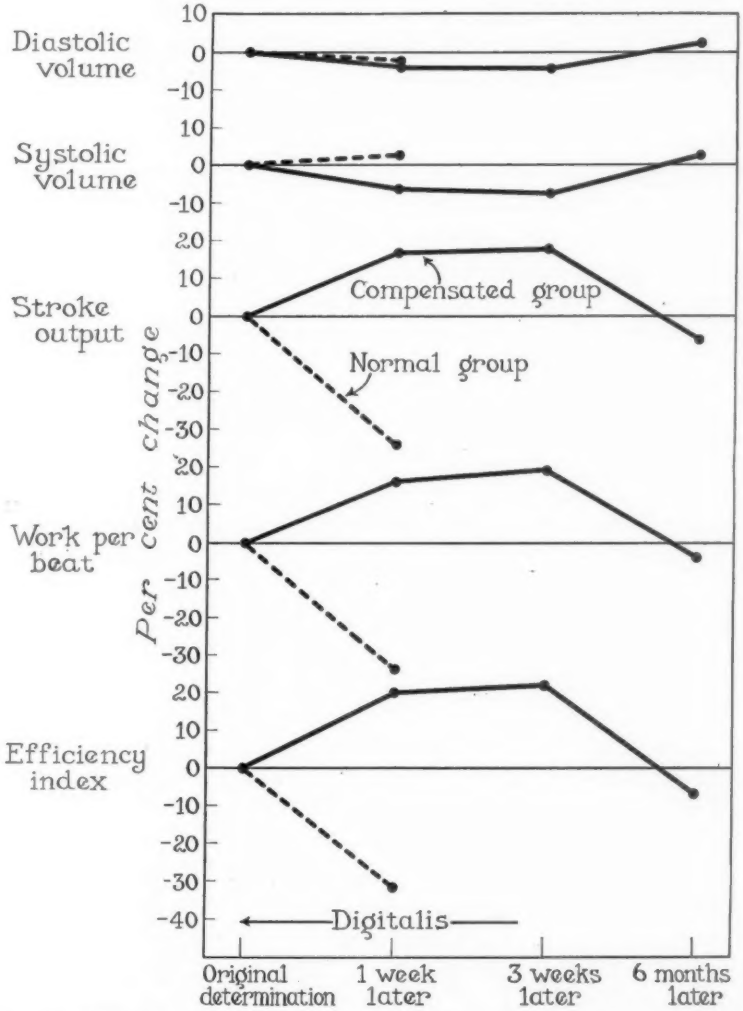

Fig. 6.—Diagram demonstrating the mean relative change in the various heart functions from original values in normal subjects and in cases of compensated heart disease during the period of digitalization. In the latter group the mean relative changes that occurred six months after the administration of digitalis had been discontinued have also been charted.

as shown in Fig. 6. In other words, the total consumption of oxygen (liberation of energy) was reduced slightly in both groups. Six months after the administration of digitalis had been discontinued, the diastolic volume of the abnormal hearts had increased slightly beyond the original volume. One will note in Fig. 6 that the systolic volume of the abnormal hearts decreased even more than did the diastolic volume, whereas the systolic volume of the normal hearts increased after digitaliza-

tion. This difference in the trends of the systolic volume of the abnormal and normal hearts after digitalization gives a clue to the mechanism by which digitalis decreases the stroke output of the normal heart and increases the stroke output of the abnormal heart.

Our observations show that, in cases in which the heart is normal, digitalis, when given in full, digitalizing doses, acts as a myocardial poison, so that the mechanical efficiency is reduced, and, therefore, the percentage of energy converted to circulatory work is decreased Inasmuch as the heart is incapable of performing as much circulatory work as it did previous to digitalization, it empties itself less completely, and, as a consequence, the systolic volume is increased and the stroke output decreased. On the other hand, in abnormal hearts a greater percentage of the available energy is converted into circulatory work, with a resultant increase in the force of systolic contraction. As a consequence, the systolic volume decreases and the stroke output increases.

The circulation time, venous pressure, and vital capacity were remeasured during the administration of digitalis. No significant changes were noted in the venous pressures, which were all within normal limits to begin with. In ten cases, the circulation time was between seventeen and twenty seconds; in eight of these cases the circulation time was less than sixteen seconds after digitalization, which is readily explained by the increase in stroke output. In all cases there was a mean increase in vital capacity of only 2 per cent after digitalization. In only two of the twenty cases in which the vital capacity was less than the predicted normal did the capacity increase to the predicted normal after the administration of lanatoside C. In the remaining cases there was either no change or a minimal decrease in vital capacity. From these observations it seems apparent that the initial reduction of vital capacity in these cases was caused by extracardiac factors.

Subjectively, the majority of the patients with compensated heart disease noted no change while digitalis was being administered. A few patients stated that physical exertion did not exhaust them as rapidly as it previously had. One patient stated that she had difficulty "catching her breath" during the first week of digitalization, but this symptom subsequently disappeared. This patient was a woman, aged 22 years, with a recently discovered aortic stenosis and insufficiency. She had an increase in her efficiency index of only 2 per cent when she was digitalized; therefore, she showed neither a positive nor a negative response to digitalization.

CONCLUSIONS

1. Of thirty-nine patients with clinically compensated, but organically diseased, hearts, thirty-four (87 per cent) showed definite improvement in mechanical efficiency when they were digitalized, whereas the remaining five, although they did not show any significant improvement, were, nonetheless, no worse after digitalization.

2. On the other hand, fourteen persons with normal hearts showed a definite impairment in cardiac function after the administration of digitalis. In these cases digitalis acted as a cardiac poison.

3. Of the eighteen patients with compensated, but organically diseased, hearts who were restudied six months after digitalization was discontinued, nine had the same cardiac function that they had before digitalization; in the remaining cases, the heart was less efficient than it had been before digitalization.

4. The degree of improvement in mechanical efficiency in cases of compensated heart disease has been correlated with circulation time. It was greatest in cases in which the circulation time was sixteen to twenty seconds.

5. The response to digitalis was essentially the same in hypertensive and rheumatic heart disease and in coronary sclerosis.

6. Digitalis exerts its action primarily on the cardiac muscle by changing the mechanical efficiency of the heart.

a. In the compensated organically diseased heart it increases the mechanical efficiency, so that a greater percentage of the total energy liberated is converted to mechanical work.

b. In the normal heart, digitalis acts as a poison and decreases the mechanical efficiency, so that a smaller percentage of the total energy liberated is converted to mechanical work.

7. It appears that every heart is endowed with the ability to work at a given mechanical efficiency which cannot be increased by digitalis unless organic heart disease has reduced this inherent mechanical efficiency, under which circumstances digitalis tends to raise mechanical efficiency toward normal levels.

8. We believe that digitalis is definitely indicated for organically diseased and enlarged hearts which appear compensated, when the circulation time, as measured by the calcium gluconate arm-to-mouth method, is greater than sixteen seconds.

9. Our studies seem to indicate that digitalis does no harm and is beneficial for many of these hearts when the circulation time is less than sixteen seconds, but since the main objective in digitalizing these patients is to increase life expectancy and physical fitness and to ward off heart failure, a long period of observation will be necessary to ascertain the ultimate benefit of digitalis.

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THE VALIDITY OF THE EINTHOVEN TRIANGLE HYPOTHESIS

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INTRODUCTION

IN RECENT work of ours, the technique and principles of augmented unipolar extremity leads were described.[1, 2, 3] Inasmuch as the use of this technique, just as with Wilson's ordinary unipolar extremity leads,[4] depends on the validity of the Einthoven triangle hypothesis, it was deemed advisable to review this latter subject and re-evaluate it, if possible.

In its barest outline, the Einthoven hypothesis may be described as follows: (1) The body is a homogeneous conducting medium.[9] Whether its shape be considered as a triangle, a circular disk, an infinite lamina, or a sphere of large or infinite radius is unimportant.[5] In this paper, it shall be considered as a sphere. (2) The electrical activity of the heart, at a given instant, may be regarded as a dipole (a + and − pole, separated by a finite distance). (3) The dipole is located in the center of the sphere. (4) The extremities (right upper, left upper, and left lower) may be considered as linear extensions of three points on the periphery of the sphere. They lie on the same plane as the dipole (corresponding to the frontal plane of the body), and are so located that, if they were to be joined by straight lines, they would form the apices of an equilateral triangle, in the center of which would be the dipole. This, in essence, is the Einthoven triangle concept.*

If this is so, certain corollaries may be deduced:

1. The algebraic sum of the potentials of the extremities, at a given instant, must equal zero. This is illustrated in Fig. 1, *a*. In Fig. 1, *a*, if the vector (the arrow) indicates the magnitude and direction of the electrical activity of the heart at a given instant, the potential at the left arm (*LA*) is equal to $\frac{K \cos \theta}{r^2}$, where k is a constant, r the distance of the electrode to the center of the dipole, and θ the angle made by a line drawn from LA to the center of the dipole and the (+) pole of the vector. The potential at *RA* is therefore $\frac{K \cos (\theta + 120°)}{r^2}$, and the potential at the left leg (*LL*) $\frac{K \cos (\theta + 240°)}{r^2}$. Since the values of

Work done under a Fellowship of the Martha M. Hall Foundation.

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Received for publication June 2, 1944.

*The Einthoven equation, Lead II = Lead I + Lead III does *not*, however, depend on the validity of the above concept[6] (see Appendix).

k and r^2 are the same for the three points, they may be disregarded. Irrespective of what the actual value of angle θ is, the sum of $\cos \theta + \cos (\theta + 120°) + \cos (\theta + 240°)$ always equals zero. For example, in Fig. 1, *a*, the value of angle θ is approximately 90°. The potentials of the extremities would therefore be:

$$LA = \cos 90° = 0$$
$$RA = \cos 210° = \cos - 30° = -.87$$
$$LL = \cos 330° = \cos + 30° = +.87$$
$$\text{and} \quad 0 + .87 + (-.87) = 0.$$

2. Any two points (on the same plane of the sphere) separated by an angle of 180° will have potentials of the same magnitude but of opposite polarity. An example will make this clear:

In Fig. 1, *b*, the potentials of points *A* and *B* are as follows:

$A = \cos \theta$

$B = \cos (180° - \theta)$.

Since θ is 120°, $180° - \theta$ is 60°. The cos 60° is ½; and cos 120° is $-\frac{1}{2}$.

3. Since the magnitude of the potential of any point (on the periphery of the sphere) varies with the cosine of the angle formed by a line drawn from the point to the center of the dipole and its positive pole, there will be two points of equal maximum potential, but of opposite polarity. These, of necessity, will be located so that they make angles of 0° and 180°, respectively, with the dipole.

4. Since this is so, the following indirect method can be used to find these two points of maximum potential: If any point, *P*, be taken on the surface of the sphere (lying on the same plane as *RA*, *LA*, and *LL*), and if the potential difference between *P* and every other point on the surface of the sphere in this plane be ascertained (as with the electrocardiograph), the largest (+) deflection, *irrespective of its actual value*, and the deepest (−) deflection, *irrespective of its actual value*, will be derived from the two points of equal maximum potential but of opposite polarity. Fig. 1, *c*, illustrates this. Assume that *P* has a potential of −2 units. If *P* and *G* are connected to the electrocardiograph and the potential difference measured, it will be found to be +5.6 (−2 − [−7.6]). Similarly, $P - H = +8$, $P - I = +4.7$, $P - J = -2$, $P - K = -9.6$, $P - L = -12$, $P - M = -8.7$, and $P - N = -2$. The maximum (+) value is +8, formed by the potential difference between *P* and *H*. The maximum (−) value is −12, formed by the potential difference between *P* and *L*. The actual values of points *H* and *L*, as can be seen in Fig. 1, *b*, are −10 and +10, respectively.

5. As a final corollary, it should be emphasized that, according to the Einthoven concept, the dipole and the extremities lie on the same plane (the frontal plane of the body, which divides the body into anterior and posterior portions). Consequently, the potentials of any vector passing in a direction at right angles to the frontal plane (i.e., anteriorly

or posteriorly) will be without effect on any point on the frontal plane, including the extremities. The reason for this is that all points on the frontal plane form an angle of 90° with such a vector (and cos 90° = 0) (Fig. 1, *d* and *e*).

The use of the indifferent electrode of zero potential, employed by the author to obtain unipolar leads, depends on the validity of corollary 1, namely, that the algebraic sum of the extremity potentials at any given instant equals zero. Similarly, if the points of maximum equal potential but of opposite polarity were to be found and joined together to a central terminal, the potential at this terminal would also be zero, according to Kirchkoff's Law.[1] (In Fig. 1, *c*, the value at such a terminal would be equal to $\frac{+10 - 10}{2} = 0$.) Therefore, electrocardiograms taken with either of these two methods should be identical if the postulates of the Einthoven concept are valid. It was this method that we used in the following study of the validity of the Einthoven hypothesis.

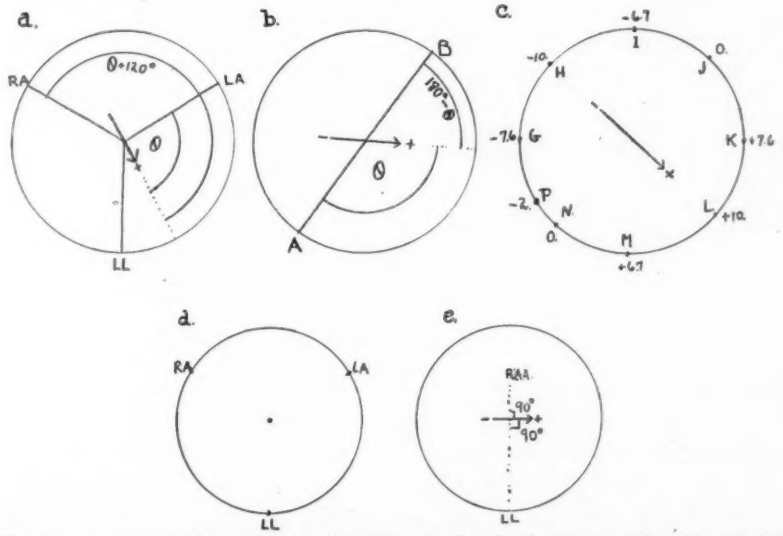

Fig. 1.—*a*, The relations of the extremities to the dipole representing the electrical activity in the heart. *RA*, right arm; *LA*, left arm; *LL*, left leg; the arrow represents a dipole. For further details see text. *b*, The relations of any two points separated by an angle of 180° to the dipole. For details see text. *c*, The potentials of varying points on the surface of the sphere lying on the same plane as the dipole. For details see text. *d*, and *e*, The effect of a dipole which points in a direction at right angles to the plane of the extremities. In *d*, the dipole may be considered as pointing inward, away from the reader. In *e*, the sphere is viewed from the right side. The full magnitude of the vector (the arrow) can now be seen. For further details see text.

METHOD

Our procedure was as follows: The subject either sat or reclined. The right arm was arbitrarily chosen as a fixed point. The electrocardiograph was set for Lead I. The right arm lead wire from the electrocardiograph was connected to the electrode on the right arm, and the left arm lead wire from the electrocardiograph was connected to another electrode which was placed on varying portions of the body (all lying on the frontal plane). It was not necessary to take records from every

point on the frontal plane of the body. As a rule, we placed the wandering electrode in the right axilla, in the right supraclavicular fossa, on the head (the electrode was arbitrarily placed at the angle of the right jaw, inasmuch as all points on the head have practically the same potential[7]) in the left supraclavicular fossa, on the left arm (Lead I), in the left axilla, at the left midaxillary line at successive points, beginning at the level of the fourth intercostal space anteriorly and proceeding to the lower level of the ribs; on the left leg (Lead II), and at varying points along the right midaxillary line.

The records taken with the wandering electrode at each of these points recorded the difference of potential between the potential of the right arm (the fixed point) and the potential of any of the points just described. With these records the electrocardiograph was standardized so that a deflection of 1 cm. represented a potential of 1 millivolt. After the records were taken, they were immediately developed and studied.

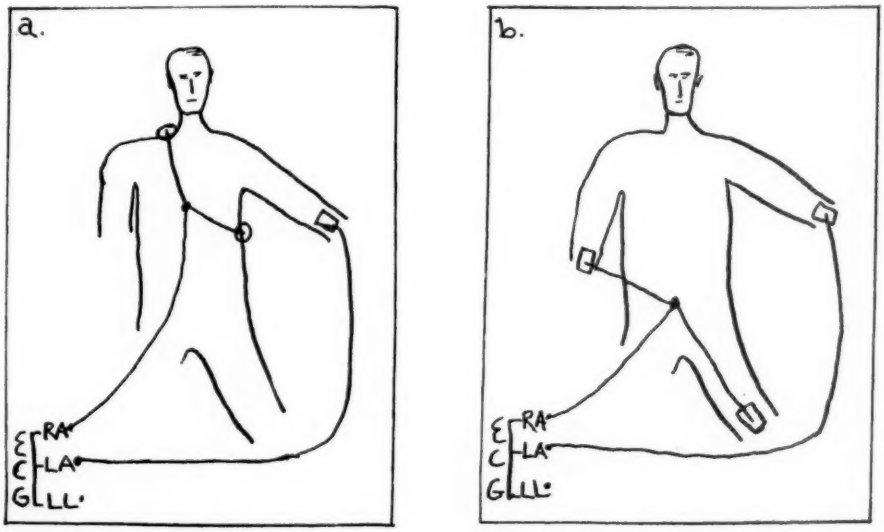

Fig. 2.—*a*, Hookup to take a record from the left arm, using as an indifferent electrode two points of maximum potential (as ascertained by the method described in the text). *b*, Hookup to take a record from the left arm, using the author's method of obtaining augmented unipolar extremity leads.

The points from which the largest (+) deflection (irrespective of its actual value), and the deepest (–) deflection (irrespective of its actual value) were thereby obtained. Electrodes were reapplied to these two regions and connected together by means of an ordinary copper wire shunt (Fig. 2, *a*). These joined electrodes were then used as an indifferent electrode, and records were taken from the right arm, left arm, and left leg (Figs. 3 and 4). In these records, the electrocardiograph was so standardized that a deflection of 1.5 cm. was equivalent to a potential of 1 millivolt. After this was done, the unipolar extremity records were taken from the right arm, left arm, and left leg, using the author's technique of obtaining augmented unipolar extremity leads.[1] With this method the records obtained are three-halves of their actual magnitude, even when the electrocardiograph is standardized in the usual manner. The augmented unipolar extremity lead records were then com-

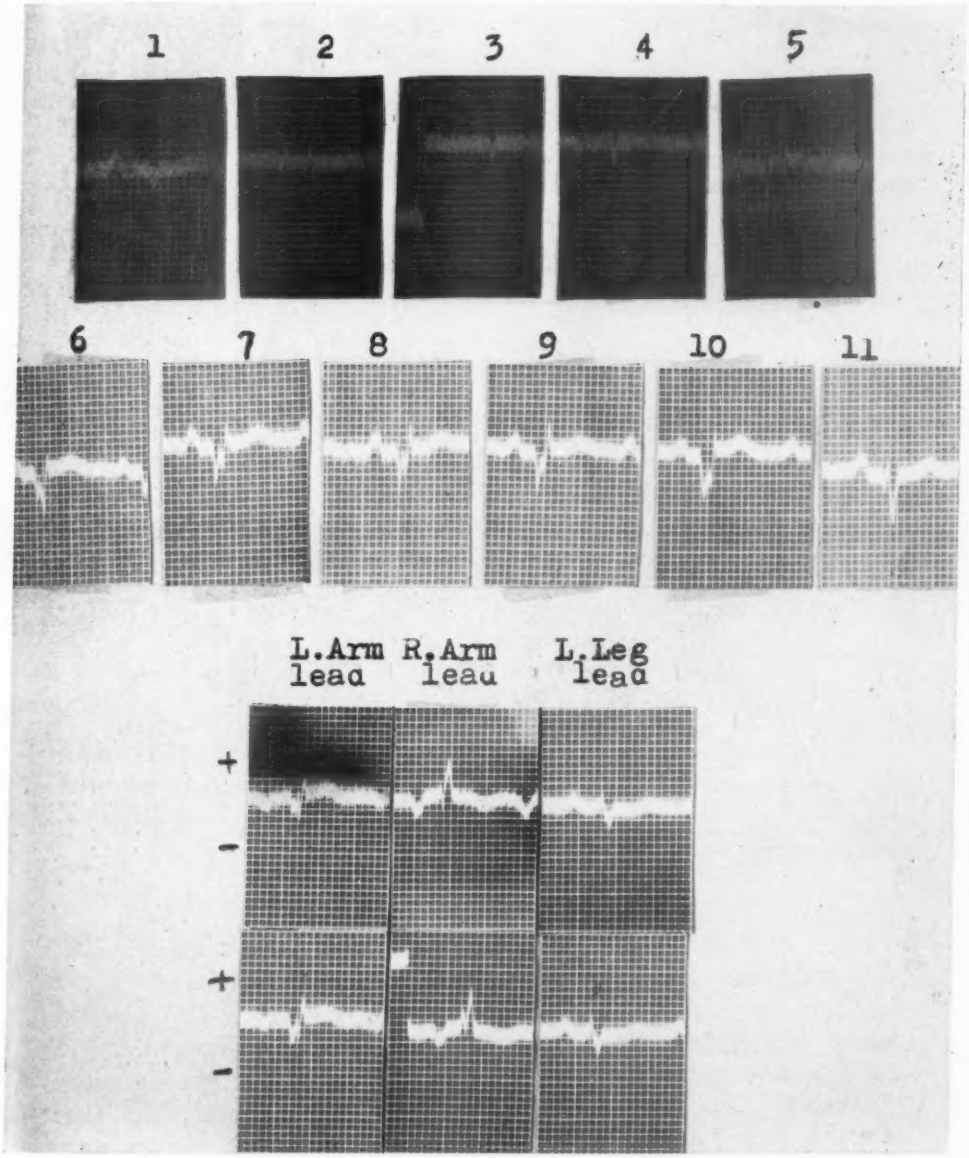

Fig. 3.—Case 1. Points *1* to *11* represent the electrocardiograms derived by using the connections of Lead I, but, instead of having the left arm lead wire on the left arm, placing it on various points, as follows: *1*, right midaxillary line at level of third intercostal space (anteriorly); *2*, right axilla; *3*, right supraclavicular fossa; *4*, head (electrode at the right angle of jaw); *5*, left supraclavicular fossa; *6*, Lead I (left arm); *7* to *10*, points along the left midaxillary line; *11*, Lead II (left leg). The upper row of extremity leads (left arm, right arm, and left leg leads) was obtained by connecting points *2* and *11* to form an indifferent electrode. These records were taken with the electrocardiogram at three-halves normal sensitivity. The lower row of extremity leads record the augmented unipolar extremity leads.

pared to the extremity records which were taken with the two points of maximum (+) and (−) potential as the indifferent electrode.

MATERIAL

Ten cases, selected at random from patients in the hospital, were studied. Among these were five with normal electrocardiograms, three with the patterns of left ventricular preponderance, and two cases of myocardial infarction.

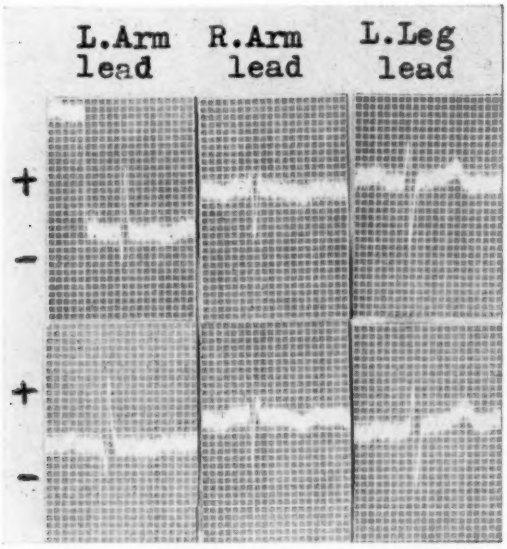

Fig. 4.—Case 2. Upper row, extremity leads obtained by using as an indifferent electrode two points on the body, namely, the right supraclavicular fossa and the left midaxillary line at the level of the sixth intercostal space anteriorly (these two points were determined by the method described in the text). Lower row, the augmented unipolar extremity leads.

RESULTS

Our technique was, at best, relatively crude, inasmuch as it is difficult at times to ascertain exactly the midaxillary line, and because slight variations in position, especially in the left midaxillary line near the heart, will sometimes cause considerable change in the potential. In spite of this, and the small number of subjects studied, the constancy of the results is significant. Figs. 3 and 4 show two examples. Case 1 was that of a 54-year-old white man who suffered from extensive myocardial infarction. The three standard leads had a downwardly directed QRS and low voltage, indicating the extensive myocardial damage.[8] In this case the distribution of polarity was just the opposite of that which is encountered ordinarily in either normal subjects or in cases of heart disease because here the largest (+) deflection was found in the right axilla (point *2*, Fig. 3), and the deepest (−) deflection was found in the left leg (point *11*, Fig. 3). (In the normal the right upper half of the body usually has a [−] potential and the left lower half of the

body usually is [+].[7]) Notice how not only the character of the QRS complexes but of the RS-T segment deviations and T waves are identical.

Case 2 was that of a 62-year-old white man with moderate hypertension. In this instance the largest (+) deflection was found in the left midaxillary line at the level of the sixth intercostal space, and the deepest (−) potential in the right supraclavicular fossa. These two points were joined to form a central terminal, and the records shown in the upper row of Fig. 4 were then recorded. These are compared to the augmented unipolar extremity leads (Fig. 4, lower row).

DISCUSSION

One of the characteristics of unipolar extremity leads, as obtained by the author's method, is the fact that, even if the indifferent electrode does *not* have a potential of zero, the algebraic sum of the potentials of the records obtained from the three extremities will equal zero. This is merely due to construction. Thus, the right arm lead actually records the difference of potential between the right arm and the mean potential of the left arm and left leg, or $RA - \frac{LA + LL}{2}$. Similarly, the left arm lead records $LA - \frac{RA + LL}{2}$ and the left leg lead, $LL - \frac{RA + LA}{2}$. The sum of these three leads is

$$\left(RA - \frac{LA + LL}{2}\right) + \left(LA - \frac{RA + LL}{2}\right) + \left(LL - \frac{RA + LA}{2}\right) =$$

$$2RA - LA - LL + 2LA - RA - LL + 2LL - RA - LA = 0$$

A similar situation holds if Wilson's original technique is used. Here the three extremities are joined to form a central terminal. The sum of the extremity potentials so recorded is:

$$\left(RA - \frac{RA + LA + LL}{3}\right) + \left(LA - \frac{RA + LA + LL}{3}\right) +$$

$$\left(LL - \frac{RA + LA + LL}{3}\right) =$$

$$3RA - RA - LA - LL + 3LA - RA - LA - LL + 3LL - RA - LA - LL = 0$$

Therefore, the characteristics of unipolar extremity leads, as recorded, cannot be used as a criterion of the accuracy of the Einthoven triangle hypothesis.

With respect to the method of proof advanced in this paper, the problem resolves itself into the question: "Is the fact that the mean potentials of the points of maximum (+) and (−) potential are equal to the mean potential of the extremities also due to construction, or is it actually a manifestation of the validity of the Einthoven hypothesis"? With respect to the answer to this, maximum (+) and (−) potentials can be obtained whether or not the body is a homogeneous conductor, whether or not the electrical activity of the heart is a dipole or some complex battery, whether or not the center of this electrical activity lies in the center of the body, and whether or not the extremities are equi-

distant from each other or from the dipole. The mean potential of these two points may or may not equal zero. If zero, it will be either because the conditions of the Einthoven hypothesis exist, or as a fortuitous result.

Similarly, any three points, other than the extremities, may be selected and joined to a central terminal. The potential of this central terminal also may or may not equal zero. Its value will be zero either because the conditions of the Einthoven hypothesis exist, or fortuitously.

The mean potential of the points of maximum (+) and (−) potential and the mean potential of the three extremities can therefore equal each other as a consequence of only three conditions: 1. The Einthoven triangle hypothesis is invalid, and the equality of values is a matter of coincidence. 2. The Einthoven hypothesis is invalid, but such other conditions exist to cause the equality to be maintained. In such a case, the values of each would either be (+) or (−), and only zero fortuitously. 3. The Einthoven hypothesis is valid, and both values are zero.

With respect to the first condition, the equality of values may be the result of coincidence in an isolated case, but it is difficult to conceive of coincidence as a determining factor when more than one case is studied. With respect to the second condition, it might be possible to devise a theoretical system in which such a relationship would hold regularly, although we have not been able to do so. Therefore, it may be said that the equality of values is *not* due to construction, but is a manifestation of the validity of the Einthoven hypothesis.

It may be pointed out that it is not necessary to get the maximum values of the P and T waves (which vary independently of the QRS complex), because, as is demonstrated in corollary 2 and Fig. 1, *b*, *any* two points separated by an interval of 180° will record potentials equal in magnitude but opposite in polarity.

CONCLUSIONS

The use of the system of unipolar leads devised by Wilson and by the author depends on the proposition that the algebraic sum of the potentials of the extremities at a given instant always equals zero. This can only be so, however, if conditions within the body correspond to the postulates of the Einthoven triangle concept which were described in the text. However, direct proof of this is impossible because, irrespective of whether the hypothesis is valid or not, the algebraic sum of the extremity potentials, as obtained in the electrocardiogram, equal zero. This, as was pointed out, is a result of construction. However, if the Einthoven concept is valid, another corollary can be deduced, namely, that every two points on the surface of the body lying on the same plane as the source of electrical activity and separated by an angle of 180° have values equal in magnitude but opposite in polarity. By means of this corollary, the points of maximum equal potential, but of opposite polarity, can be obtained, theoretically and actually. Since the

mean potential of these two points equals zero if the Einthoven hypothesis is valid, extremity records obtained by using these two points as an indifferent electrode can be compared with the usual unipolar extremity lead records. Our observation that records so obtained and compared are identical allows us to conclude that the Einthoven hypothesis is valid, as is our method of obtaining unipolar leads.

APPENDIX

Lead II = Lead I + Lead III because of construction, and bears no relation to the validity of the Einthoven hypothesis.[6] It is due to the fact that, in Lead III, the connection of the left arm to the electrocardiograph is the reverse of its connection in Lead I. Therefore, Lead III records the difference of potential between the left arm and left leg, viz., LA – LL, whereas, in Lead I, the difference of potential between the right and left arms is recorded RA – LA. If these two leads are added together, the values of the LA cancel each other out, RA – LA + LA – LL = RA – LL, which is Lead II.

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EFFECT OF ATROPINE UPON THE PROLONGATION OF THE P-R INTERVAL FOUND IN ACUTE RHEUMATIC FEVER AND CERTAIN VAGOTONIC PERSONS

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IT HAS been suggested that a physiologic dose of atropine will shorten the P-R interval in heart block due to vagotonia and fail to do so in the heart block found in rheumatic fever. As a result of this conception, atropine has been used as a diagnostic test in cases of heart block, to differentiate between vagotonia and rheumatic fever. This practice has more or less persisted, even though Bruenn[1] showed, in 1937, that atropine shortened the prolonged P-R interval to normal in nineteen of twenty-two cases of acute rheumatic fever. In my experience with this procedure, it was soon observed that atropine did shorten the prolonged P-R interval in rheumatic fever, as observed by Bruenn, as well as in vagotonic persons. Inasmuch as many rheumatic fever cases and a fair number of vagotonic patients with prolonged P-R intervals were available, a comparative study was undertaken to ascertain definitely the value of atropine as a test to differentiate between the prolonged P-R interval of the vagotonic subject and the rheumatic fever patient.

PROCEDURE

Group 1.—Seventy-seven patients who had active rheumatic fever and whose electrocardiograms showed a P-R interval of 0.21 second, or longer, were studied. The patients were divided into two subgroups. Group 1A consisted of forty-three patients. They were given the following test: A control electrocardiogram was taken in the supine position, the patient was then given $\frac{1}{75}$ grain of atropine subcutaneously, and electrocardiograms were made at 20, 40, 60, and 120 minutes after the administration of atropine. It was found in this group (Group 1A) that the maximum shortening of the P-R interval occurred at the end of twenty minutes. In Group 1B, therefore, consisting of thirty-four patients, the same test was given with the exception that only a control tracing and one twenty minutes after the atropine were taken. The patients were kept flat in bed during the test period.

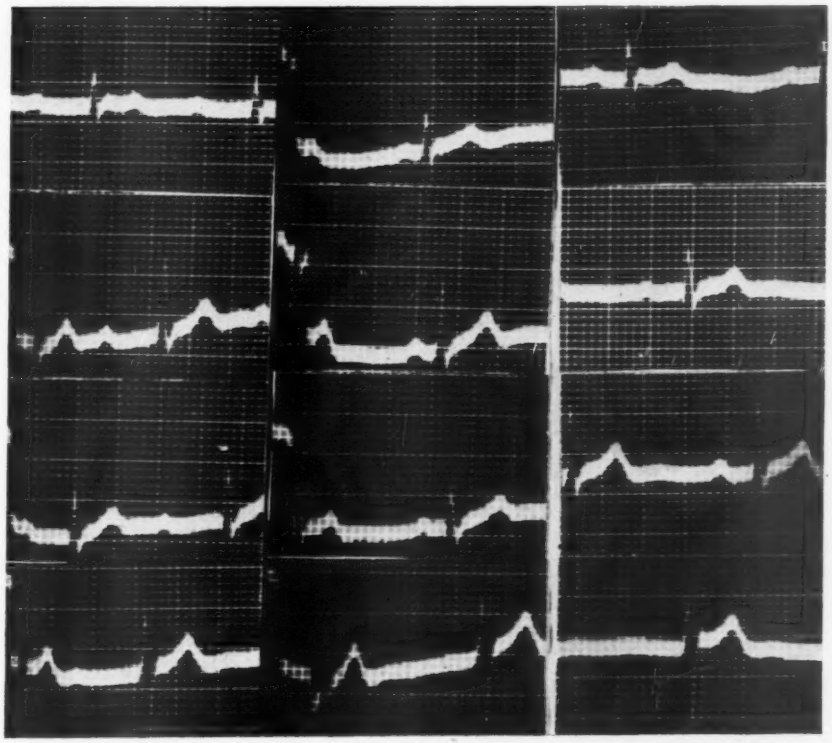
Group 2.—This group consisted of twelve vagotonic persons with prolonged P-R intervals. They were chosen to compare with Group 1, and were subjected to the same procedure as described previously.

RESULTS

Group 1.—Group 1A was observed over a two-hour period after $\frac{1}{75}$ grain of atropine. The P-R interval ranged from 0.21 to 0.32 second. Shortening of the P-R interval occurred in all of the forty-three cases and varied from 0.02 to 0.18 second (Fig. 1). The average shortening of the P-R interval for the entire group was 0.05 second. The maximum

Received for publication June 8, 1944.

shortening of the P-R interval occurred 20 minutes after giving the atropine in twenty-three cases, and 40 minutes after in twenty cases. The P-R interval returned to the control duration within 40 minutes after the atropine in one instance, within 60 minutes in seven cases, and within 120 minutes in seventeen cases. In the remaining cases, the P-R interval was still shorter than the control reading at the end of two hours.



a *b* *c*

Fig. 1.—*a*, Shows a P-R interval of 0.30 second in a case of acute rheumatic fever. *b*, Tracing taken twenty minutes after 1/75 grain of atropine subcutaneously. The P-R interval has been shortened to 0.14 to 0.16 second. *c*, Two hours after the atropine the P-R interval is prolonged slightly to 0.20 to 0.22 second.

Group 1B was followed over a twenty-minute period after $\frac{1}{75}$ grain of atropine. The P-R intervals ranged from 0.21 to 0.36 second. Shortening of the P-R interval occurred in each of the thirty-four cases in this group, and varied from 0.02 to 0.14 second, with an average of 0.047 second.

By combining Groups 1A and 1B, seventy-seven patients with rheumatic fever showed an average shortening of the P-R interval of 0.049 second after $\frac{1}{75}$ grain of atropine hypodermically. Fig. 2 shows the maximum shortening of the P-R interval in each case in this group.

There was no significant effect on the QRS interval after giving atropine. In the cases which were followed over a two-hour period there

were some rather unexpected effects upon the heart rate. The rate was increased in thirty-three, unchanged in two, and definitely slower in seventeen cases. There were frequent, transient variations in the amplitude and direction of the P waves after the atropine. There was a definite decrease in the amplitude of P_2 and P_3, and occasionally P_1, of short duration, in twenty-one of these cases. P_3 was inverted, temporarily, in seven instances. In one case, P_1, P_2, and P_3 became inverted

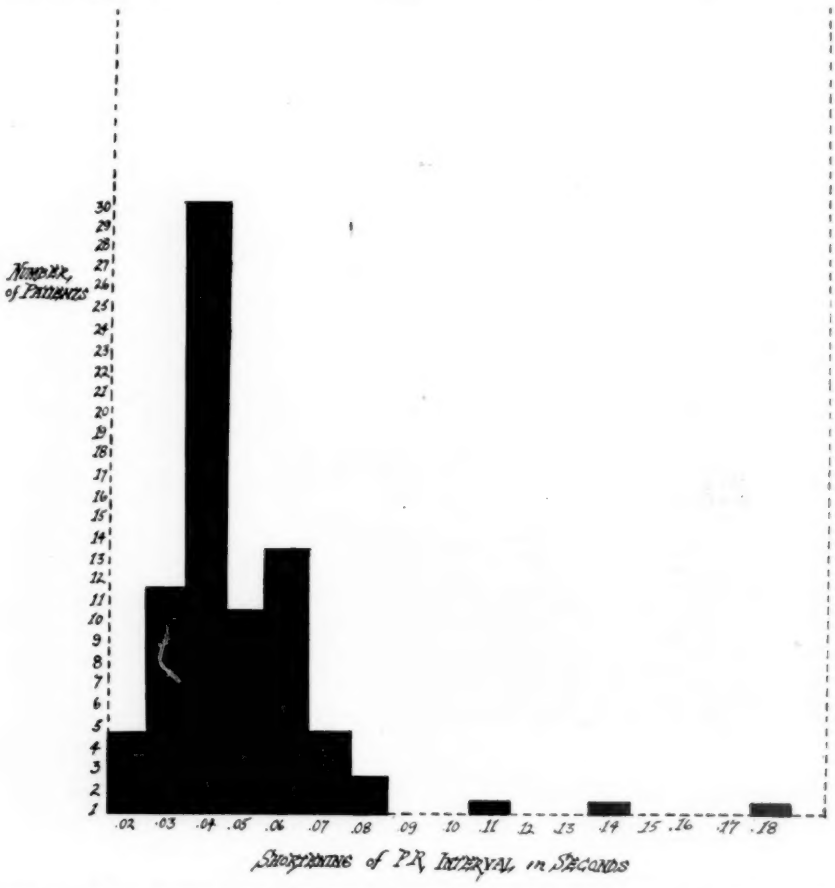
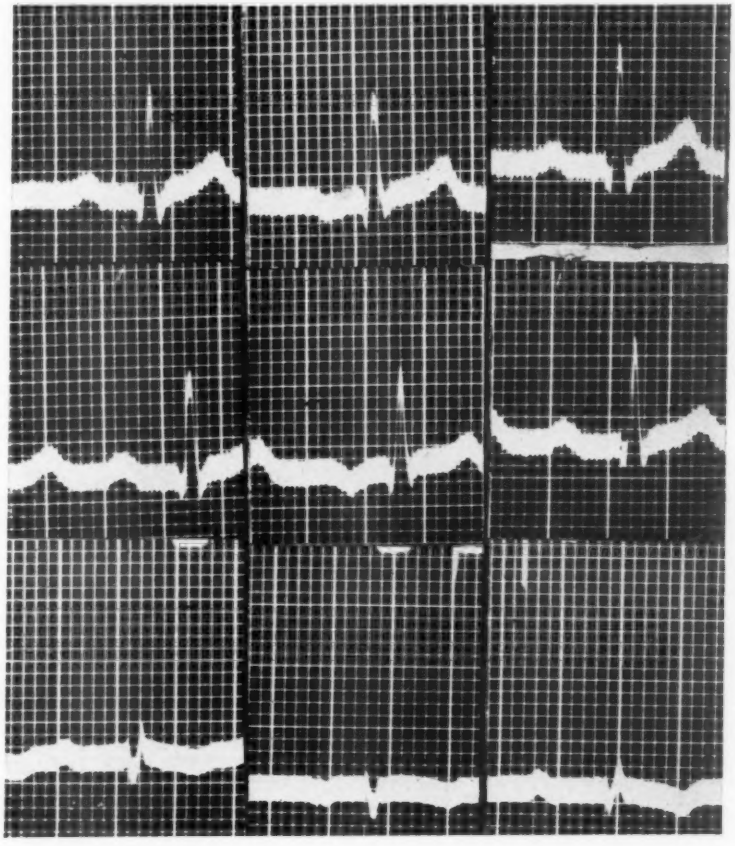


Fig. 2.—Chart showing the maximum shortening of the P-R interval in each of the seventy-seven cases in this study of rheumatic fever patients.

for a short time during the experiment (Fig. 3). There was no significant effect on the P waves in the remaining cases. Two patients with P-R intervals of 0.24 and 0.23 second, respectively, had temporary nodal rhythm twenty minutes after $\frac{1}{75}$ grain of atropine subcutaneously.

In analyzing the cases used in this study, it became apparent that a majority of the patients were coming under observation after they had had rheumatic fever for more than two months. This was because patients in the acute stage of the disease were being retained in Station

Hospitals until it became evident that prolonged hospitalization would be necessary. For the purpose of ascertaining whether or not atropine shortened the P-R interval in the more acute stages of rheumatic fever, as well as in the subacute stage, the patients were classified according to whether they had been under observation during the first six weeks of their rheumatic fever or after two months. There were nineteen cases in which the atropine test was done during the first six weeks. The average shortening of the P-R interval in this group was 0.052 second.

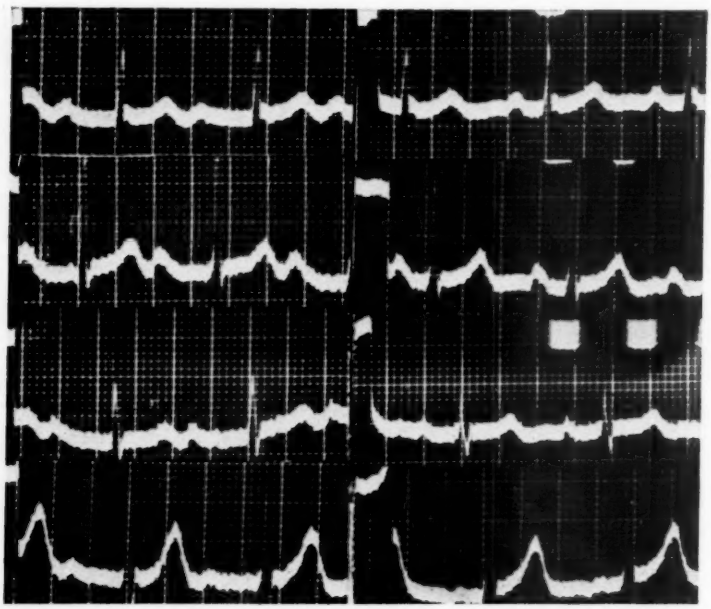


a *b* *c*

Fig. 3.—*a*, Patient with acute rheumatic fever and a P-R interval of 0.24 second. *b*, The same patient, forty minutes after 1/75 grain of atropine subcutaneously, shows inverted P waves in Leads I, II, and III and a P-R interval of 0.18 to 0.19 second. *c*, Two hours after the atropine, the P waves are again upright and the P-R interval has returned to the control level of 0.24 to 0.26 second.

There were fifty-three cases in which the atropine test was done sometime between the second and ninth month of active rheumatic fever. The average duration of the disease in these cases was three and one-half months. The average shortening of the P-R interval in this group was 0.043 second. It is obvious from these studies of the two groups of cases that atropine shortens the P-R interval in both the very acute

stages of rheumatic fever and in the following months of subacute activity, as long as the P-R interval is prolonged. It is in this latter group of cases that a test capable of differentiating between heart block produced by vagotonia and active rheumatic fever would be of definite benefit. In many cases the only sign of activity of rheumatic fever may be prolongation of the P-R interval months after the acute joint symptoms and fever have subsided. If the acute stages of the rheumatic fever were so mild as not to be recognized, it would be difficult to interpret prolongation of the P-R interval which was first detected several months after the onset of the disease.



a *b*

Fig. 4.—*a*, This patient had neurocirculatory asthenia and marked vagotonia. P-R interval was 0.36 second before atropine. *b*, Twenty minutes after 1/75 grain of atropine subcutaneously the P-R interval was 0.20 second.

Group 2.—In order to ascertain whether there is any material difference in the reaction of rheumatic fever patients and vagotonic persons to atropine, a group of twelve vagotonic subjects with prolongation of the P-R interval was studied with the atropine test over a two-hour period. The age of these patients ranged from 18 to 34 years. Only one was over 26 years of age. There was no history of rheumatic fever, chorea, diphtheria, or the consumption of a drug in any case. There were no symptoms of degenerative heart disease. The blood pressure was normal in every instance. The heart was of normal size on physical examination and roentgenologically in each case. There were three that had soft, "functional," systolic murmurs in the pulmonic area. The temperature and sedimentation rates were normal. All presented the typical

clinical picture of neurocirculatory asthenia with vagotonia. The P-R intervals ranged from 0.22 to 0.34 second. The atropine test on these patients resulted in a shortening of the P-R interval in each case, ranging from 0.04 to 0.16 second, with an average of 0.075 second (Fig. 4).

Although the average shortening of the P-R interval in these vagotonic cases was more marked than in those of rheumatic fever, the difference was not great enough to differentiate between the two conditions.

SUMMARY

1. Seventy-seven cases of active rheumatic fever with P-R intervals of 0.21 second, or longer, were studied. A control electrocardiogram was taken. The patients were then given $\frac{1}{75}$ grain of atropine subcutaneously, and subsequent tracings were taken at 20 minutes in thirty-four cases, and at 20, 40, 60, and 120 minutes in forty-three cases. There was shortening of the P-R interval in each instance, ranging from 0.02 to as much as 0.18 second. The average shortening of the P-R interval for the entire group was 0.049 second. These observations confirm those of Bruenn.[1] A temporary period of nodal rhythm was observed twenty minutes after the atropine in two cases. There was no significant effect on the interventricular conduction time. There was a transient effect upon the amplitude and direction of the P waves in twenty-nine cases, with a decrease in the amplitude of P_2 and P_3 in twenty-one cases, transient inversion of P_3 in seven cases, and temporary inversion of P_1, P_2, and P_3 in one case. The heart rate increased after atropine in thirty-three cases, diminished in seventeen, and remained unchanged in two cases.

2. Twelve vagotonic persons who had prolonged P-R intervals were also given the atropine test. There was shortening of the P-R interval in each case after atropine, ranging from 0.04 to 0.16 second, with an average of 0.075 second.

CONCLUSION

From these observations it seems clear that atropine cannot be used to differentiate between the prolongation of the P-R interval caused by vagotonia, on the one hand, and rheumatic fever, on the other, for the P-R interval is shortened by atropine in both of these conditions. These experiments present additional evidence that impairment of auriculoventricular conduction in acute rheumatic fever is due, in part at least, to an increase in vagal tone, as Bruenn[1] has suggested.

I wish to thank Colonel James S. Sweeney, M.C., Army of the United States, for his helpful interest and encouragement in carrying out this study.

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THE EFFECT OF EXPERIMENTAL CORONARY ARTERY LIGATION ON THE COENZYME I AND COCARBOXYLASE CONTENT OF THE MYOCARDIUM OF THE DOG

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IT HAS been shown that breakdown of intracellular coenzymes occurs in shock and anoxia, and that this breakdown can be remedied by the administration of the corresponding vitamins.[1, 2] With this work as a background, we thought it would be interesting to investigate another important condition involving tissue anoxia, namely, that of coronary occlusion. When experiments on coronary ligation were begun, cocarboxylase was estimated in normal and ischemic cardiac muscle, as will be described, but no significant changes were demonstrable, contrary to the results obtained in previous studies of other tissues in shock.[1] When coenzymes other than cocarboxylase were considered, the fact that the heart is unable to metabolize lactate after coronary occlusion[3] suggested that coenzyme I, or diphosphopyridinenucleotide, the coenzyme of lactic dehydrogenase, might be destroyed. Since lactate is the preferential carbohydrate substrate for heart muscle,[4-6] a breakdown in its metabolism may be of importance from the standpoint of the viability of the ischemic cells. The fact that nicotinic acid deficiency produces electrocardiographic changes which are remediable by nicotinic acid administration[7] and are strikingly similar to electrocardiographic disturbances produced by coronary artery ligation[8] is further suggestive evidence that anoxia may produce coenzyme breakdown in heart muscle as well as in other tissues.

In order to ascertain whether or not such destruction of coenzymes does occur, both cocarboxylase and coenzyme I were estimated in normal and ischemic heart muscle, with and without the administration of nicotinamide, riboflavin, and succinate. The results of these experiments are presented here.

METHODS

Dogs which had been kept on a stock diet of Pard dog food for two weeks were anesthetized with pentobarbital sodium, administered intravenously. Under positive pressure artificial respiration the chest was opened via a midsternal incision, and the left anterior descending coronary artery exposed. In some cases the artery was dissected free and ligated, and in others a suture was passed beneath artery and vein, ligating both. (As will be seen, this apparently made no difference in

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This investigation was aided by a grant from the Dazian Foundation.
Received for publication June 10, 1944.

the coenzyme changes noted.) After this, the chest was closed by suturing.

In some experiments therapeutic agents were administered thirty minutes before the operation, in others, one hour after the ligation. In all cases, two hours after ligation of the vessel or vessels, the chest was reopened, the heart excised, and samples of myocardium removed from the ischemic area and from near-by normal areas of the left ventricular muscle.

These samples were quickly weighed, plunged into beakers of boiling water, and boiled for five minutes, after which the beakers were placed in a pan of ice water. After cooling, the samples were minced with scissors, homogenized, and the suspensions centrifuged. The supernatant fluid was analyzed for cocarboxylase* by the manometric method already described,[1] and for coenzyme I by the method of Axelrod and Elvehjem.[9] In some cases apozymase for the latter method was made by the method of Greig[2] from bottom yeast,† and in others apozymase was prepared from baker's yeast by our carbon tetrachloride method.[10]

The hearts of all dogs were examined after the muscle samples had been removed, in order to ascertain the amount of occlusion of the artery. Those animals in which the artery was found patent were discarded. Electrocardiograms taken on a few of the animals after the operation showed unmistakable evidence of coronary occlusion.

RESULTS AND DISCUSSION

Table I shows the results obtained in six experiments in which the left anterior descending coronary artery was ligated, with and without ligation of the accompanying vein. It will be seen that a consistent breakdown of coenzyme I occurred, varying in magnitude from 70 to 83 per cent of normal. No consistent change occurred in cocarboxylase, however. The importance in the metabolism of cardiac muscle of such a destruction of coenzyme I has already been pointed out.

TABLE I

CONTROLS

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
7A	Artery	1,533	358	-76.6	77.4	44.8	-42.2
7B	Artery	1,737	394	-77.4	43.7	47.4	+ 7.8
8A	Artery and vein	2,090	603	-71.2	76.8	57.4	-25.3
8B	Artery and vein	2,595	442	-83.2	88.3	79.4	-10.1
9A	Artery	1,749	517	-70.6	52.5	47.0	-10.5
9B	Artery and vein	2,750	674	-75.5	64.3	73.0	+13.5
			Average	-75.7		Average	-11.1

Mann and Quastel[11] have shown that nicotinamide inhibits coenzyme I nucleotidase, the enzyme which breaks down coenzyme I in damaged brain tissue. It seemed logical to try this substance in order to reduce the amount of breakdown shown in Table I. Table II shows the result

*Cocarboxylase for use as reference standard in these estimations was kindly supplied by Merck and Company.

†Kindly supplied by Dr. Greig.

TABLE II

NICOTINAMIDE AFTER LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
14A	Artery	1,263	259	-79.5	42.3	41.4	- 2.1
14B	Artery	2,155	747	-65.4	52.4	48.9	- 6.7
16B	Artery	2,425	1,173	-51.7	26.3	30.9	+17.5
18A	Artery and vein	2,950	2,162	-26.7	31.8	47.4	+49.1
18B	Artery and vein	2,210	767	-65.3	45.0	47.3	+ 5.1
			Average	-57.7		Average	+12.6
			$t = 2.16$	$p = > .05$			

of the administration of 20 mg. of nicotinamide intravenously per kilogram of body weight one hour after the coronary artery had been ligated. It may be seen that there was apparently some decrease in coenzyme I breakdown when nicotinamide was administered after tying the vessel; the average breakdown was 57.7 per cent, but this decrease is not sufficiently marked to be statistically significant.

It occurred to us that perhaps the drug might not be reaching the ischemic area, for the heart muscle was rendered anoxic very suddenly, probably before significant collateral circulation could be established. Consequently, several dogs were given nicotinamide before the vessels were ligated. The results of these experiments may be seen in Table III.

After pretreatment with nicotinamide there was definitely less breakdown of coenzyme I; the average amount of breakdown was 31.8 per cent, as against 75.7 per cent in the controls. This difference is statistically significant ($p = < .01$).

Greig[2] has shown that, in shock, alloxazine adenine dinucleotide, the riboflavin containing coenzyme, is destroyed. This coenzyme is known to be necessary for the oxidation of reduced coenzyme I. Acting on the supposition that alloxazine adenine dinucleotide may also be destroyed in coronary occlusion, riboflavin (5 mg. per kilogram of body weight) was administered with nicotinamide to four dogs before coronary

TABLE III

NICOTINAMIDE BEFORE LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
19B	Artery	1,820	1,570	-13.7	----	----	----
20A	Artery	2,850	644	-77.4	24.7	29.2	+18.2
20B	Artery and vein	1,930	1,412	-26.9	42.8	35.7	-16.6
21A	Artery	2,340	2,620	+12.0	32.3	33.0	+ 2.2
21B	Artery and vein	3,310	2,710	-18.2	32.5	28.8	-11.4
22A	Artery and vein	3,755	2,085	-44.5	32.5	40.7	+25.2
22B	Artery	3,725	1,830	-50.8	30.9	30.7	- 0.6
			Average	-31.8		Average	+ 2.8
			$t = 3.68$	$p = < .01$			

TABLE IV

RIBOFLAVIN AND NICOTINAMIDE BEFORE LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
24A	Artery and vein	4,090	3,300	-19.3	32.0	37.3	+16.6
25A	Artery and vein	1,862	1,105	-40.6	27.5	35.6	+29.4
25B	Artery	1,690	1,050	-37.8	31.0	34.2	+10.3
26A	Artery and vein	2,190	1,424	-35.0	37.7	41.3	+ 9.5
			Average	-33.2		Average	+16.5
			$t = 9.57$	$p = < .01$			

ligation. Although these experiments showed 33.2 per cent breakdown of coenzyme I, which was slightly more than the amount after pretreatment with nicotinamide, there was much less variation among the dogs receiving both vitamins, and the difference was statistically much more significant (p = much less than .01).

Succinic acid is a C_4 dicarboxylic acid which can be metabolized directly by the cytochrome-cytochrome oxidase system without the help of the coenzymes discussed previously. Thus, the administration of this substrate might be supposed to supply sufficient energy to keep the cell intact, and perhaps to allow resynthesis of some of the coenzymes broken down in anoxia. Proger[12] has demonstrated an increase in oxygen uptake by homogenized heart muscle in the presence of succinate, even in an atmosphere of reduced oxygen tension. He also points out that succinate is often able to prevent anoxic electrocardiographic changes in dogs.

We have administered sodium succinate (1 Gm. per kilogram of body weight) intravenously to dogs, before and after coronary ligation. As may be seen in Tables V and VI, there was a significant reduction in coenzyme I breakdown ($p = < .01$) when the substance was given before ligation; the average breakdown was 39.3 per cent. When injected after coronary occlusion, the amount of breakdown averaged 48.7 per cent, which is statistically only moderately significant ($p = < .05$).

TABLE V

SUCCINATE AFTER LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
11A	Artery and vein	2,860	2,705	- 5.3	53.8	57.1	+ 6.1
12A	Artery	2,400	1,319	-45.4	44.9	45.6	+ 1.6
12B	Artery	2,340	725	-68.2	44.8	52.0	+13.9
13A	Artery	2,860	1,039	-63.7	37.7	34.3	- 9.0
13B	Artery and vein	1,940	414	-78.6	33.7	30.1	-10.7
15	Artery	3,050	2,100	-31.1	28.7	28.6	- 0.3
			Average	-48.7		Average	+ 0.3
			$t = 2.40$	$p = < .05$			

TABLE VI

SUCCINATE BEFORE LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
28A	Artery and vein	2,090	1,229	-41.2	29.5	33.4	+13.2
23A	Artery	2,365	697	-70.6	31.3	38.8	+24.0
23B	Artery and vein	2,345	1,187	-49.4	28.7	25.1	-12.6
27A	Artery and vein	1,700	1.695	- 0.3	33.3	40.2	+20.7
27B	Artery	3,510	2,285	-34.9	35.7	35.7	0
			Average	-39.3		Average	+ 9.1
			$t = 3.46$	$p = < .01$			

It will be noted that the control levels of cocarboxylase in these hearts were quite high, compared to those reported previously for other tissues. Also, one is surprised to see that no consistent change in cocarboxylase occurred under the experimental conditions reported here. That synthesis of cocarboxylase can go on in ischemic heart muscle, provided other coenzymes are reasonably intact, is suggested by Table IV, which shows that the ischemic sample in all four animals contained more cocarboxylase than did the control sample. Possibly the sluggish circulation in the ischemic muscle may have contributed to this by preventing the washing out of free nicotinamide, riboflavin, and thiamine.

Although we have presented evidence here that the administration of nicotinamide, riboflavin, and succinate can prevent the breakdown of coenzyme I which follows coronary ligation, it remains to be shown that these substances produce a beneficial effect on cardiac function after such a procedure. This problem, together with analyses of other possible metabolic failures in experimental coronary occlusion, is being investigated.

SUMMARY

1. Coenzyme I is destroyed to the extent of 70 to 83 per cent of normal in cardiac muscle rendered ischemic by coronary artery ligation.

2. Nicotinamide, nicotinamide and riboflavin, and succinate, when administered intravenously before coronary ligation, protect to a great extent against such breakdown of coenzyme I.

3. Nicotinamide and succinate are only fairly efficient in remedying this destruction when injected after the occlusion has been established.

4. No significant change in tissue cocarboxylase occurs after coronary ligation.

The author wishes to express his gratitude to Dr. Herbert S. Wells and Dr. Tinsley R. Harrison for their very helpful criticism and suggestions.

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THE EFFECT OF DIATHERMY ON CORONARY FLOW

An Experimental Study on Dogs

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During the past thirty years numerous articles have reported the beneficial results of diathermy in the treatment of angina pectoris. In 1911, Nagelschmidt[1] reported a small series of patients with angina pectoris who apparently were definitely improved after a series of treatments with high frequency current. Nagelschmidt concluded this report by saying, "It is most remarkable to see how patients in a very grave condition recover immediately under the influence of diathermy. In a few seconds or minutes all trouble ceases, no oppression, no pain, no restlessness, no feeling of anguish." Again, in 1928, Nagelschmidt[2] indicated his enthusiasm when he stated, "I do not know of any other medicament or any other method which would be able to cut off so severe an attack in so very few moments of application as with diathermy." Stewart,[3] in 1926, reported, "There is no question that diathermy through the heart will improve the coronary circulation and minimize the effect of toxin on its muscular structure." Laubry, Walser, and Meyer,[4] in 1937, reported their results with diathermy in the treatment of angina pectoris. Of the fifty-six patients so treated, 40 per cent obtained very good results, and 20 per cent, fair results. They pointed out that short waves were much superior to long waves, and that best results were obtained in angina of effort. Wolf,[5] in his textbook of physical therapy, states, "If we take into consideration the physiological action of diathermy, that it raises the temperature of the tissue and thus dilates vessels, we can a priori state that it will be helpful in all those cases of angina pectoris which are due to a narrowing of the coronary vessels, be it by sclerotic process or by spasms." Siegen[6] treated 770 patients with angina pectoris, employing short wave diathermy in addition to other routine forms of therapy, and reported his results in 1937. Forty-three per cent of the 770 patients were reported as cured, 54 per cent were improved, and only 3 per cent were uninfluenced. In addition to the subjective improvement noted by the patients, he presented serial electrocardiograms which showed "evident improvements." Similarly, Hyman[7] treated 87 patients with symptoms of coronary thrombosis and noted "improvement" in the electrocardiogram, as well as improvement clinically after a series of diathermic treatments. Blackman and Richardson[8] stated that short wave

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Received for publication June 16, 1944.
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diathermy is the most efficient and reliable agent available for improving the blood supply to the myocardium in cases of coronary thrombosis, and they felt that clinical evidence shows that diathermy allays spasm, induces coronary dilatation, and develops new blood pathways. Ferrario[9] states, "In general, patients with the syndrome of angina pectoris improve notably under short wave treatment." Hay and Ince,[10] Joslyn,[11] Brow,[12] Cignolini,[13] and many others have reported favorably on this type of treatment. Bearman,[14] on the other hand, points out that it is difficult to prove that there is any special value in the use of the short wave current in the treatment of angina pectoris because spontaneous remissions occur in the disease and because rest and other measures are applied concurrently.

It is evident that the majority of reports are enthusiastic about the beneficial effects of diathermy on symptoms attributed to coronary insufficiency. These reports, however, are confined for the most part to clinical observations or electrocardiographic interpretation.

The purpose of this study was an attempt to ascertain experimentally the effect of diathermy on coronary flow in the dog.

As a preliminary experiment, the temperature of the heart muscle of the dog after applying diathermy over the heart was measured. A thermocouple was inserted into the musculature of the right ventricle through the opened chest wall. The chest was then tightly closed. The control temperature was 96.2° F. for a period of ten minutes. Diathermy was then applied over the precordial region for one-half hour. Immediately after this application, the temperature rose to 104° F. This elevation in temperature was accounted for by the heating of the thermocouple in the high frequency induction field. One-half minute temperature readings were recorded to secure a cooling curve during the next three minutes, and at the end of this time the temperature had fallen to what was probably a true level, namely, 102.3° F. This result indicated that the temperature of the heart was elevated by the application of diathermy through the chest wall.

The coronary flow was measured on the intact animal, using the technique described by Gilbert and Fenn.[15] Despite past criticism of this method, we felt that it was most applicable to the problem under consideration.

Dogs weighing 13 to 14 kilograms were used. One-half hour before operation the animals were given 0.25 c.c. of a 4 per cent solution of morphine sulfate per kilogram of body weight. Grehant's mixture (5 per cent chloroform in 50 per cent alcohol) was given a few minutes before operation by means of a stomach tube. The anterior chest wall was opened at the right costochondral junction. The parietal pleura was opened, and oxygen was administered by means of a tracheal cannula under positive pressure to prevent atelectasis. The coronary sinus was then cannulated with a modified Morovitz cannula which was connected to the cylinder of a piston recorder. With a known volume of the

cylinder, the volume of the blood flow was readily calculated. Heparin was used to prevent coagulation. The blood was returned by way of the femoral vein and kept at a constant rate of flow, temperature, and pressure. The blood pressure was recorded from the carotid artery by a mercury manometer. (Typical curves obtained are shown in Figs. 1 and 2, taken from Dog 4, Table I.)

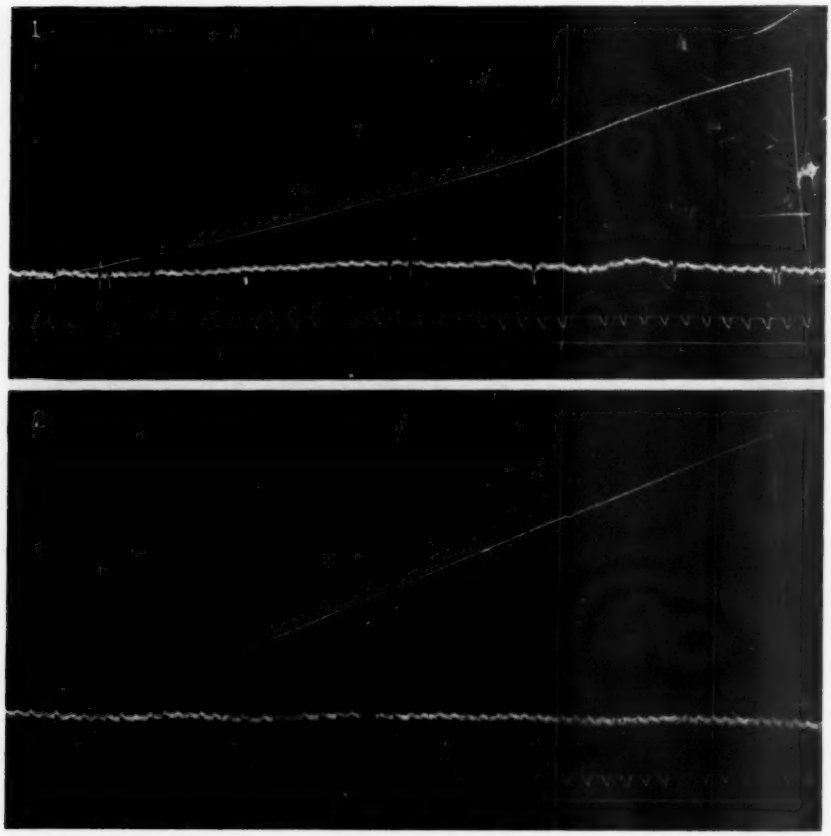

Fig. 1.—The slowly rising gradient represents the rise of blood in the cylinder of the piston recorder. When the cylinder becomes full it is emptied manually, and thus the rapid fall. The vibratory line represents the blood pressure recording. The automatic timer was set at five seconds. Graph *1* represents coronary flow at the start of the experiment. In the middle portion of this tracing there is a rather sharp rise in the gradient. At this point theobromine was injected intravenously, and the rise indicates that there is an increase in the coronary flow and that the cannula is in the coronary sinus and is functioning properly. Graph 2 is the control curve, taken two minutes after theobromine injection and just prior to application of the inductotherm.

After the coronary flow had become stabilized, an 8-inch inductotherm disk[16] was placed on the precordial area. Several thicknesses of burlap were placed between the chest wall and the disk to act as a dielectric. The machine was arbitrarily set at 100[16] and applied for one-half hour. Eleven animals were used for the experiment, four of which were controls. In two of the controls no heat was applied, in the third a hundred-

watt electric light bulb was used as a source of heat and placed over the precordial area for one-half hour, and, in the fourth, the inductotherm disk was placed over the lower part of the abdomen.

The results are summarized in Tables I and II. It will be noted that, of the animals which received diathermy over the precordial area (Table I), there was an increase in the coronary flow in all except one, in which there was a slight decrease. It would thus appear that the short wave

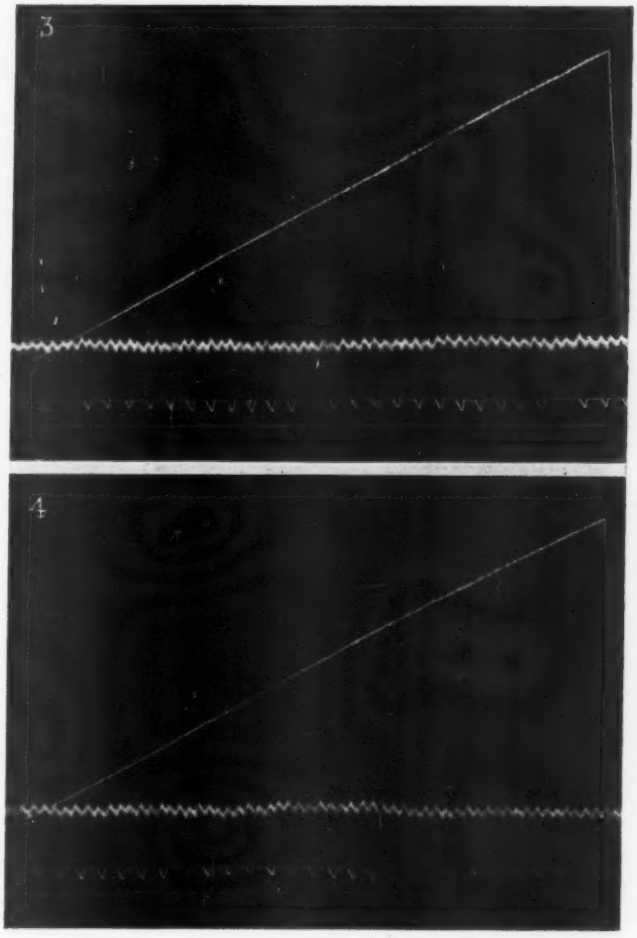

Fig. 2.—Graphs *3* and *4* represent coronary flow after one-half hour of application of the inductotherm over the precordial area. It is evident that coronary flow has increased over the control.

current increased coronary flow. However, in the controls there was also an increase in the coronary flow which was as marked as when diathermy was applied to the heart itself.

In some instances this increase could be explained by an increase in heart rate as noted in Dogs 1, 2, 4, 5, and 7, in Table I, and Dog 3 in Table II. In Dogs 4 and 5, Table I, there was a rise in blood pressure

TABLE I

DIATHERMY OVER PRECORDIAL AREA FOR ONE-HALF HOUR

DOG	CORONARY FLOW (C.C./MIN.)	BLOOD PRESSURE (MM. HG)	HEART RATE PER MINUTE	
		Control readings		
1	25.2	34/30	159	
2	7.2	42/35	96	
3	13.2	35/29	150	
4	19.8	28/25	114	
5	17.4	26/24	108	
6	18.0	19/16	130	
7	14.5	27/23	93	
		Readings at the end of experiment		CHANGE IN CORONARY FLOW (C.C./MIN.)
1	28.8	22/20	220	3.6+
2	21.6	19/16	132	14.4+
3	18.0	30/21	135	4.8+
4	28.8	32/28	144	9.0+
5	22.2	29/22	120	4.8+
6	20.4	19/17	135	2.4+
7	12.6	26/22	111	1.9-

TABLE II

CONTROL ANIMALS

DOG	CORONARY FLOW (C.C./MIN.)	BLOOD PRESSURE (MM. HG)	HEART RATE PER MINUTE	
		Control readings		
1	13.5	48/45	117	
2	10.8	34/21	75	
3	20.7	49/44	145	
4	18.0	31/26	142	
		Readings at end of experiment		CHANGE IN CORONARY FLOW (C.C./MIN.)
1	22.2	29/26	105	8.7+
2	18.0	27/24	66	7.2+
3	23.4	44/42	155	2.7+
4	21.6	28/23	142	3.6+

Dog 1. Diathermy over lower part of abdomen for thirty minutes.
Dog 2. 100-watt electric light bulb over precordial area for thirty minutes.
Dogs 3 and 4. No heat applied. Final readings taken one-half hour after control readings.

which could have produced an increase in coronary flow. In Dogs 3 and 6, Table I, and Dogs 1, 2, and 4, Table II, the increase in the coronary flow could not be explained by either changes in the blood pressure or the heart rate. This increase in flow was apparently due to the development of acidosis, as suggested by Gilbert and Fenn.[15, 17]

CONCLUSION

1. The effect of applying diathermy over the heart on the coronary flow of the dog was measured.

2. As measured by this method, no significant increase in the coronary flow was demonstrated.

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SUGAR TOLERANCE IN NEUROCIRCULATORY ASTHENIA

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IN MAY, 1943, when we were seeing a large number of soldiers with neurocirculatory asthenia, we first became impressed with the marked similarity between the symptoms of neurocirculatory asthenia and those of hypoglycemia. This report covers a study of the glucose tolerance curves which was carried out over the ensuing seven months at Torney General Hospital. There is one striking difference in the histories of patients with neurocirculatory asthenia and those with true hypoglycemia, namely, the regular occurrence of the latter several hours after meals, and prompt relief with the ingestion of carbohydrates, and the absence of such a history in neurocirculatory asthenia. Dorst[1] carried out a similar study in 1936. He found that the person with neurocirculatory asthenia had a flat tolerance curve, whereas the sthenic type had a normal curve. He further demonstrated that the former type of person gained weight, and rapidly developed a normal tolerance curve on insulin therapy. His further work demonstrated a similar, flat curve in neurasthenic persons in general. He believes the flat curve is common enough to be of diagnostic value in the "Effort Syndrome," and suggests that the continued low blood sugar level may account for the characteristic asthenia in this group.

The report herewith rendered is in large part confirmatory of Dorst's results, although we do not agree that the low sugar values are responsible for the asthenia. This disagreement is based on three facts: Not all the patients who suffer from typical neurocirculatory asthenia have low values; none of the symptoms, including asthenia, is improved at any time by the administration of sugar; one patient in our group with typical neurocirculatory asthenia had diabetes mellitus with high blood sugar values.

This report covers the study of forty patients. Each patient was thoroughly examined from a clinical and laboratory standpoint, including chest roentgenogram, electrocardiogram, blood cholesterol, basal metabolic rate, heart rate while asleep, urine concentration and urea clearance, blood cell count, urine, Kahn reaction, and numerous blood pressure readings. Heart disease and hyperthyroidism were adequately excluded in all cases. Every patient had symptoms and signs typical of neurocirculatory asthenia, consisting of shortness of breath, sharp precordial pain, palpitation, "blackouts," asthenia, headache, poor appetite, tachycardia when awake, tremor, marked dermographism, and hyperhidrosis, particularly of the hands, feet, and axillae.

Six-hour glucose tolerance tests were done on all patients; a fasting specimen was followed by hourly specimens for six consecutive hours after the oral administration of 100 Gm. of glucose, except in seven of

Received for publication June 18, 1944.

the cases, in which five specimens were examined at hourly intervals. One of these seven had a diabetic curve. The other six were the earliest ones done, and since the curve was still falling at the end of four hours, we decided to prolong the test on later ones. In all but seven of these thirty-two cases, the level at six hours was greater than at five hours. In five of these the reading was the same as at five hours; in one it was 2 mg., and, in the other, 7 mg., lower. The Folin Wu technique was used for the carbohydrate estimations.

Curves were classed as low if the highest single reading was under 140 mg. per cent. Of the forty patients, twenty-six, or 65 per cent, were classified as having low curves. The highest level attained in these twenty-six cases is shown in Table I.

TABLE I

BLOOD SUGAR LEVEL MG. PER CENT	NUMBER OF CASES
131-140	1
121-130	7
111-120	5
101-110	5
91-100	5
81-90	3

In most of the curves with peaks of 120 or more, there was only one such reading, and the rest of the curve was below 100. Eleven had normal curves, two were questionably diabetic, and one was definitely diabetic.

Several of the patients were given candy when they felt weak or faint, but in no instance did this procedure improve the faintness, even temporarily. Furthermore, there was no relationship between eating and the appearance of "blackout" spells. Sometimes these spells would come on immediately, or shortly, after a meal rich in carbohydrate.

COMMENT

This study is confirmatory of Dorst's work. A flat tolerance curve is present in a sufficiently high percentage of cases to be of value in the diagnosis of neurocirculatory asthenia. The explanation of this is not immediately apparent, but, in our opinion, the low sugar levels do not cause the symptoms in this psychoneurotic syndrome. Dorst has further shown that a similar curve is present in other psychoneuroses.

CONCLUSIONS

Sixty-five per cent of forty patients with typical symptoms of neurocirculatory asthenia showed flat sugar tolerance curves. It has been found that the test is of some value in confirming the diagnosis, but, in our opinion, the low sugar levels are not responsible for the symptoms.

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Clinical Reports

PAROXYSMAL AURICULAR TACHYCARDIA DUE TO RECIPROCAL RHYTHM

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THE mechanism of re-entry is believed to explain an extrasystole which is firmly bound to a preceding beat, coming always after a fixed interval. De Boer[1] invoked re-entry as an explanation of extrasystoles, and Lewis[2] agrees that single extrasystoles may be due, on occasion, to re-entry. Lewis also states that re-entry is possible in the auricle, A-V node and the ventricle, accounting for auricular, nodal, and ventricular extrasystoles. Another form of re-entry is reciprocal rhythm, i.e., an impulse is conducted from the A-V node or ventricles to the auricles, finds an auricular by-pass, and is transmitted again to the ventricles. Katz[3] asserts that reciprocal rhythm should be diagnosed only when two ventricular complexes within 0.5 second of each other have a bizarre P interposed between them. A mechanism of this nature, he asserts, can conceivably continue for some time and give rise to a tachycardia which is similar in all respects to supraventricular tachycardia. We have recently studied a case which illustrates the above mechanisms and presents certain other peculiar features.

REPORT OF CASE

The patient was a 40-year-old schoolteacher who suffered from gradually progressing paraplegia of one year's duration caused by a spinal tumor which was removed at operation. For the preceding five years he had complained of very frequent spontaneous attacks of rapid palpitation, lasting for variable periods of time, ranging from minutes to a few hours, although not of a disabling nature. Clinically, simple paroxysmal tachycardia was diagnosed; it could be readily arrested by carotid sinus pressure. Digitalis in saturating doses kept the tachycardia well under control; on the other hand, quinidine (taken in 0.2 Gm. doses five times daily for a period of three days) definitely aggravated and perpetuated the tachycardia, and interfered with the otherwise prompt response to carotid sinus pressure. Electrocardiograms were taken during the tachycardia, and the effect of pressure on the right carotid sinus was demonstrated; another series was taken in the intervals of spontaneous freedom from the attacks.

Analysis of the records revealed the following peculiar arrhythmia.

Received for publication Nov. 17, 1943.
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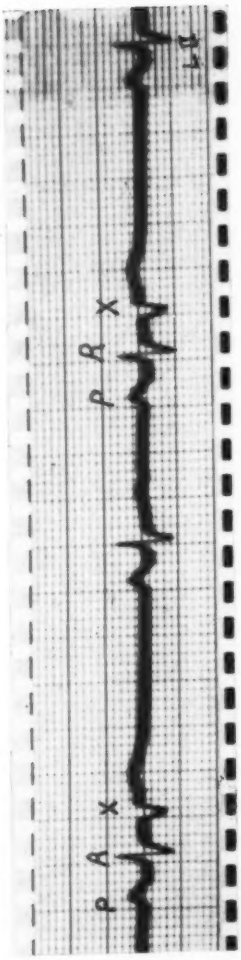

Fig. 1.—The fine vertical lines are 0.04 second apart. The distance between horizontal lines, at the standardization used, represents 0.1 millivolt. The same values apply to the other figures.

Fig. 2.

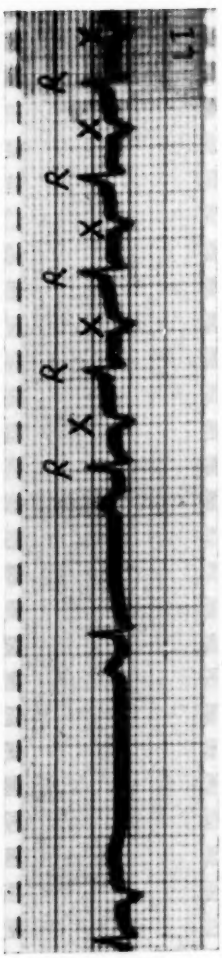

Fig. 3.

Fig. 4.

Fig. 1 shows Lead II, which was taken during one of the intervals between the paroxysms of tachycardia. It reveals normal sinus rhythm, disturbed every now and then by an auricular extrasystole which is blocked because of its prematurity.

Measurement of the P-X interval (the time from the beginning of P to the beginning of the following extrasystole) and the R-X interval (the time from the beginning of QRS to the beginning of the following extrasystole) showed that the former was 0.47 second, and the latter, 0.25 second.

Fig. 2 (Lead IVF) shows an auricular extrasystole which was conducted to the ventricle. This conduction may be accounted for by slight changes in the refractory period of the junctional tissues, enabling the impulse to pass to the ventricle and elicit a response. P is followed by R_1, and this is followed by X_1 (an auricular extrasystole), which is conducted to the ventricle (R_2); this is followed by X_2, which is blocked.

The time relations in this series are as follows: $P\text{-}X_1 = 0.46$ second, $R_1\text{-}X_1 = 0.24$ second, $X_1\text{-}X_2 = 0.52$ second, $R_2X_2 = 0.24$ second.

Fig. 3 shows Lead I during an attack of paroxysmal tachycardia, during which the X-X interval is 0.42 second, and the R-X interval, 0.24 second.

Fig. 4 (Lead I) shows spontaneous cessation of one of the attacks of tachycardia, with a blocked auricular beat. The time intervals are exactly the same as in Fig. 3.

DISCUSSION AND COMMENT

1. Consideration of the time relations shown previously will make it quite evident that there was a fixed coupling of auricular extrasystoles to preceding ventricular beats. The R-X intervals were strikingly constant (0.24 to 0.25 second), whereas the P-X and X-X intervals varied from 0.46 second to as much as 0.52 second. This fixed time relation of auricular extrasystoles to preceding ventricular beats, which implies a causal relationship, makes it difficult to avoid the conclusion that a re-entrant wave of stimulus formation from the ventricle into the auricle was responsible for the fixed coupling.

2. Further evidence of this is the interesting fact that an auricular extrasystole never followed another blocked auricular extrasystole. It would appear that an auricular extrasystole could not occur unless the impulse of the auricular beat, whether from the sinus or premature stimulus, entered the ventricle. Only when this occurred was the by-pass reached along which re-entry to the auricle could take place.

3. During paroxysms of tachycardia (Fig. 3) the X-X intervals were 0.42 second, whereas the R-X intervals were still 0.24 second, showing again the close coupling of auricular to preceding ventricular beats. The paroxysms of auricular tachycardia thus appeared to be due to re-entry through the ventricular by-pass into the auricle, leading to an auricular extrasystole, which re-entered again through an auricular by-pass, and was conducted to the ventricles; the cycle was repeated in this order for a variable period of time, until some increase in the re-

fractory period of the junctional tissues (spontaneous or induced by carotid sinus pressure) led to blocking of these auricular extrasystoles, which inevitably ended the attack.

4. Actually, when an attack ended in this case, it did so with a blocked auricular extrasystole. It is argued that, if the paroxysmal tachycardia be due to the sporadic activity of an ectopic pacemaker, cessation of the attack would occur when that ectopic pacemaker stopped its sporadic discharge. Blocking of the auricular beats would have no effect on their genesis from the ectopic pacemaker.

5. It is also interesting that digitalis, presumably by interfering with conduction of the stimulus between the auricles and ventricles, controlled the attacks well. Quinidine, on the other hand, failed in this respect quite markedly. This is not easy to explain, but it may have been due to its vagal effect, paralysis of which improves conduction, and so perpetuates the attacks.

SUMMARY

A case of arrhythmia is analyzed and discussed in detail, and evidence is offered to indicate that the following were factors in producing the arrhythmia:

1. *Blocked Auricular Extrasystoles.*—Re-entry into the auricle from a ventricular by-pass; the re-entrant waves were not transmitted back again to the ventricles.

2. *Conducted Auricular Extrasystoles.*—Re-entry into the auricles from a ventricular by-pass; the re-entrant waves were transmitted back into the ventricles, i.e., reciprocal rhythm.

3. *Attacks of Auricular Paroxysmal Tachycardia.*—A continuously circulating wave of excitation between the ventricles and auricles, i.e., reciprocal rhythm perpetuated over some length of time.

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APPARENT ARREST OF STAPHYLOCOCCAL ENDOCARDITIS

WARD J. MACNEAL, M.D., CHARLES A. POINDEXTER, M.D., NEW YORK, N. Y., AND FREDERICK N. MARTY, M.D., SYRACUSE, N. Y.

C. S., a white man, born April 5, 1907, gave a history of "kidney trouble" in 1924, for which he took a milk diet for some time. About 1932 he had a typical attack of rheumatic fever, with severe pain and swelling and tenderness in the hips, knees, and ankles. During this illness he had an acute middle ear infection. A myringotomy was performed, and thereafter he had a persistent hearing defect in his right ear. After this attack of rheumatic fever, tonsillectomy was performed. There was no recognized recurrence of rheumatic fever. During the summer of 1943, while engaged as a superintending engineer of construction work in Tennessee, he suffered from chigger bites on his lower extremities, and one of these lesions suppurated for several weeks. In October, 1943, he returned to his home in Syracuse, New York, for a short vacation.

He consulted his local physician (F. N. M.) on October 20, stating that he had felt well until the previous three or four days, when he noted soreness in the calves of both legs and lameness in his left shoulder. He also had pains in the back of his neck and an occasional headache. He had not had weakness, dyspnea, chest pain, cardiac palpitation, undue fatigue, ankle edema, or any sensation of chills and fever.

The patient was a well-developed and well-nourished man of athletic build. His temperature, as observed at home for several days, was no higher than 99.8° at any time. An aortic diastolic murmur and a loud, rough, systolic, blowing murmur were heard over the precordium, and the heart was moderately enlarged. The leucocyte count was 9,300, with 73 per cent polymorphonuclears and 27 per cent lymphocytes. The sedimentation rate was 30 mm. in an hour (Cutler method). Examination of the urine was negative. He was sent home to bed with a provisional diagnosis of mild recurrent rheumatic fever.

After three or four days of rest in bed his previous complaints disappeared entirely. He was suddenly seized, however, with sharp pain in the lower right quadrant of the abdomen, just a little to the right of the midline. Several total and differential leucocyte counts, as well as urinalysis, were done, and failed to reveal evidence of any acute inflammatory process. A local surgeon saw him in consultation at this time, but, after several days of rest in bed, the pain subsided completely. A blood culture taken Oct. 22, 1943, revealed *Staphylococcus aureus,* and blood cultures were repeated at intervals of a week until three had been taken; all were positive for *Staph. aureus.*

On Nov. 16, 1943, he was admitted to the Syracuse Memorial Hospital for further observation and treatment with large doses of sulfadiazine. He was given this drug in doses of 1.5 Gm. every four hours for five

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Aided in part by Grants No. 500 and No. 501 of the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

The penicillin used was generously supplied by Rare Chemicals, Inc., Flemington, N. J., and by Chas. Pfizer, Inc., Brooklyn, N. Y.

Received for publication Sept. 13, 1944.

days, when he developed signs of renal irritation and this drug had to be discontinued. His blood level of sulfadiazine on the last day of this therapy was 13.6 milligrams. Two subsequent blood cultures were taken, both of which failed to reveal any growth of *Staph. aureus.* He was discharged from the hospital Nov. 23, 1943. The diagnosis at this time was rheumatic heart disease, with aortic and mitral insufficiency, and *Staph. aureus* bacteremia, probably with bacterial endocarditis. The patient was transferred to New York City and admitted to the Post-Graduate Hospital on Dec. 3, 1943. The subsequent hospital record is summarized in the graphic charts.

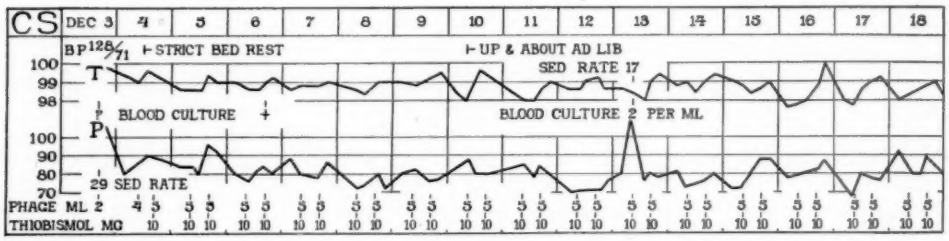

Fig. 1.

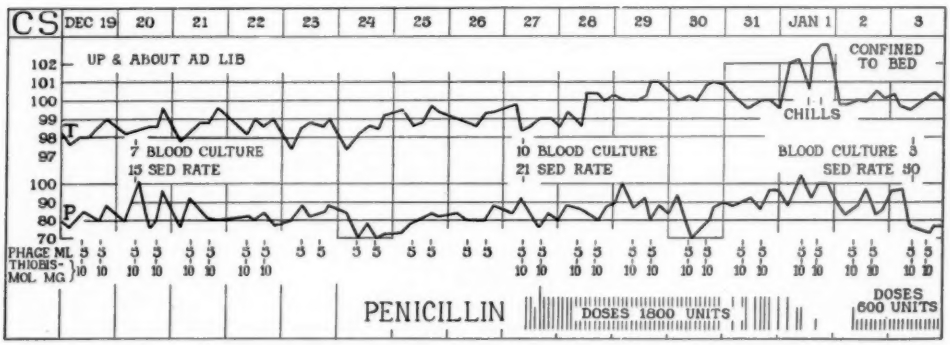

Fig. 2.

On December 3, the erythrocyte sedimentation rate was 29 mm. in an hour; the blood pressure was 128/71. A blood culture taken at this time was reported as unsatisfactory and of doubtful significance because of the growth in it of staphylococci which were considered to be contaminants. The diagnosis of staphylococcal endocarditis was not accepted as fully established. Nevertheless, a stock staphylococcus bacteriophage was administered by intravenous injection twice daily, and thiobismol was also given. The patient was confined strictly to bed until December 10, and then was allowed to be up and about until January 1. During this period, the diagnosis of staphylococcemia became established by consistently positive blood cultures taken by meticulous technique on December 6, 13, 20, and 27. The patient had been referred with the hope that he might be treated with penicillin, and he became progressively discouraged.

The penicillin which became available on December 27 was a partially purified preparation in phosphate buffer solution. It evidently contained considerable amounts of pyrogenic impurities. Intramuscular

injections of approximately 1,800 units every two hours caused pain at the injection sites, and, on December 31, the patient was no longer willing or able to accept the treatment. The chills and rise in temperature on January 1 were ascribed to the action of this preparation of penicillin. Subsequently, doses of 600 units were accepted without too much complaint, but the patient felt that he was not improving under this treatment.

On January 9 a supply of refined penicillin became available, and this was injected intravenously during the day and intramuscularly at night in doses of 5,000 units every two hours from January 9 to 18. The blood culture on January 10 showed a growth of less than one colony per milliliter of blood, and all the subsequent cultures, of which there were many, remained negative. The sedimentation rate was 50 mm. on January 3, 30 mm. on January 10, and 28 mm. on January 17. Encouraged by these signs of improvement, we continued the bacteriophage and the thiobismol, and, on January 18, increased the penicillin dose to 10,000 units every two hours and continued this dose to January 31.

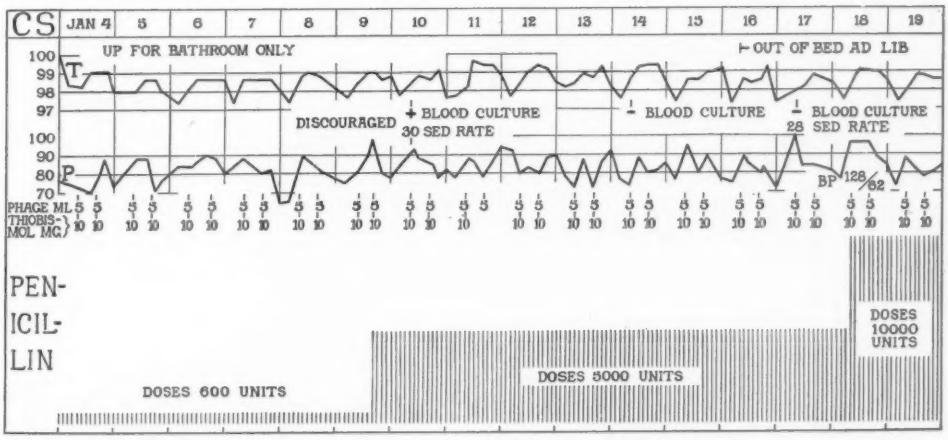

Fig. 3.

The penicillin dose, for sake of economy, was then reduced to 5,000 units every two hours from January 31 to February 21. From February 18 to 28 the thiobismol was omitted, and neoarsphenamine was administered in a dose of 10 mg. twice a day. On February 28 the thiobismol was resumed. The dose of penicillin was reduced on February 21 to 2,000 units every two hours, and finally discontinued altogether on February 28. The injections of staphylococcus bacteriophage and thiobismol were continued to March 18, when the patient was discharged from the hospital, and the injections of the bacteriophage were still being continued when this report was written (September, 1944). It will be noted that the sedimentation rate did not exceed 15 mm. per hour after January 17, and that the blood cultures remained consistently negative.

The changes in the cardiac murmur were of clinical interest, and probably of considerable significance for the diagnosis. During December there was a double mitral murmur of blowing quality, diastolic and systolic, transmitted to the left axilla. On January 18 the systolic murmur had become more loud and harsh, and was best heard at a point 2 cm. below the left nipple. This harsh sound occurred in late systole,

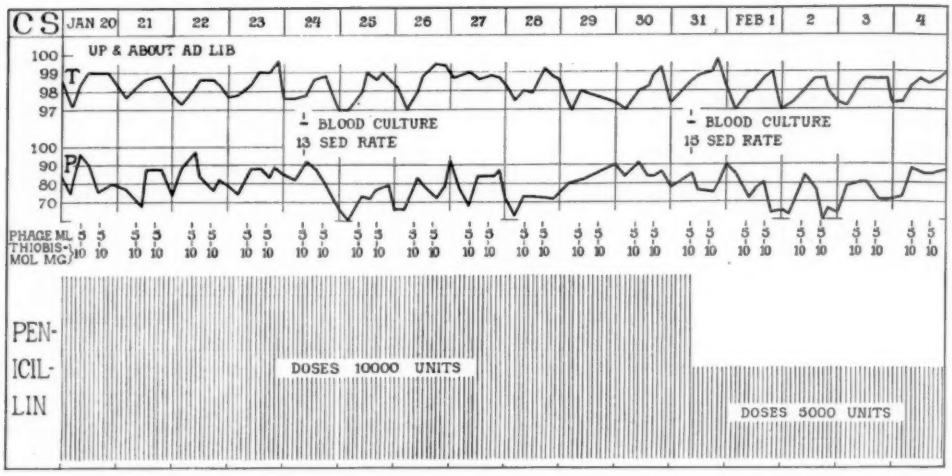

Fig. 4.

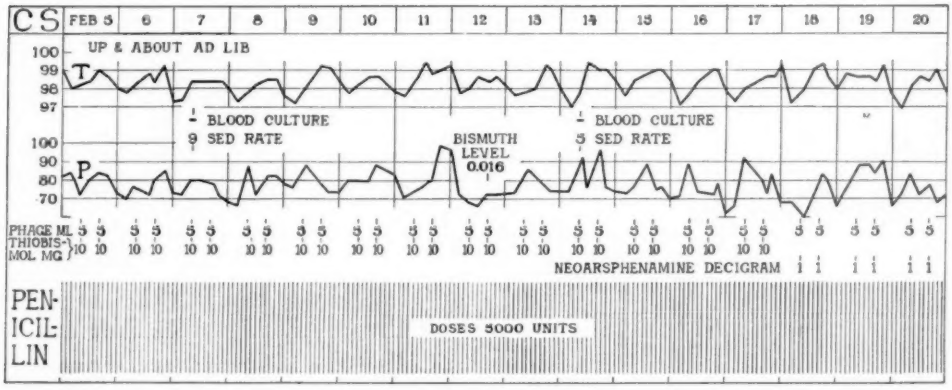

Fig. 5.

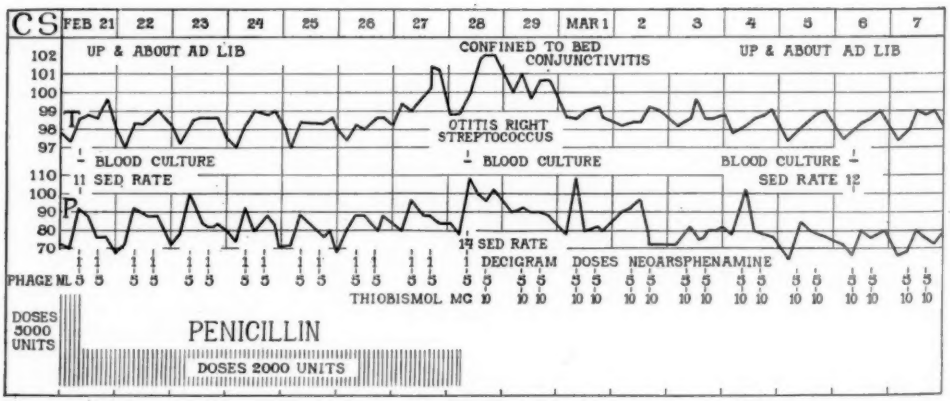

Fig. 6

and was designated by different observers as a "leathery squeak," a "late systolic bleat," and "whistling character of murmur." In the axilla the systolic murmur continued to have the earlier blowing quality. After February 1, this curious squeaky murmur became less and less perceptible. The blowing double mitral murmur persisted.

The discouraging upset which began on February 26 was evidently related to an exacerbation of the old otitis media. From the exudate from the auditory canal both a streptococcus and staphylococcus were cultured. The inflammation subsided after irrigation, and the general therapeutic program was not disturbed on this account.

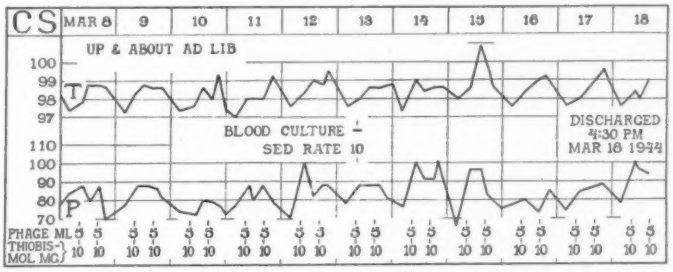

Fig. 7.

After his discharge from the hospital, on March 18, the patient remained in New York for several weeks, and was treated daily with intravenous injections of bacteriophage. He then went to his home in Syracuse, where he has been treated by Dr. Marty. He has since returned to New York City several times for physical examination, leucocyte count, blood culture, and sedimentation rate. The results of these tests have been satisfactory. The sedimentation rate in millimeters per hour was 9 on April 3; 7 on April 10; 8 on May 4; 7 on June 7; 7 on July 6; 8 on August 3; and 5 on August 8. Blood cultures taken

TABLE I

ABRIDGED DATA OF ROUTINE EXAMINATION OF BLOOD

DATE	ERYTHROCYTES (×1,000)	HEMOGLOBIN (GM.)	LEUCOCYTES	NEUTROPHILES (%)	EOSINOPHILES (%)
Dec. 4	4,400	14.5	10,050	75.5	2.0
Dec. 13	4,680	15.0	9,000	62.0	3.0
Dec. 27	4,040	12.7	8,350	70.0	3.0
Jan. 3	5,090	14.0	7,200	59.0	6.0
Jan. 10	5,330	14.0	11,650	69.0	2.0
Jan. 18	5,430	14.0	14,150	77.0	1.0
Jan. 24	5,490	15.0	9,350	67.0	2.0
Jan. 31	5,790	15.8	7,800	64.0	6.0
Feb. 7	4,470	13.5	10,250	67.0	3.0
Feb. 14	4,610	13.6	7,350	71.0	2.0
Feb. 21	4,870	14.5	7,300	62.0	6.0
Feb. 28	5,570	14.8	6,450	76.0	3.0
Mar. 6	5,020	15.0	7,050	68.0	6.0
Mar. 13	4,720	13.5	8,850	64.0	7.0
May 4	4,740	14.0	11,250	59.0	3.0
June 7	5,000	15.0	9,950	57.0	1.0
July 6	5,060	16.0	10,400	63.0	2.0

April 5, April 10, May 4, June 7, July 6, August 3, and August 8 have remained sterile. The patient has gained in strength and weight. He is now back at work.

The significant data on the blood counts are shown in Table I. No transfusions were required. Routine examinations of the urine, made weekly, revealed nothing abnormal.

CONCLUSION

We recognize that a diagnosis of staphylococcal mitral endocarditis may be disputed in the absence of an anatomic and cultural study of the cardiac valves themselves. Nevertheless, it is our considered opinion that this patient* actually suffered from bacterial mitral endocarditis caused by infection with *Staphylococcus aureus,* and that the disease is now in a stage of arrest, which may possibly be permanent.

*The patient was still in excellent condition, with a persistent mitral murmur, on Jan. 11, 1945.

Abstracts and Reviews

Selected Abstracts

Crismon, J. M.: Effect of Hypothermia on the Heart Rate, the Arterial Pressure and the Electrocardiogram of the Rat. Arch. Int. Med. 74: 235, 1944.

The effects of hypothermia on the heart rate, the arterial pressure, and the electrocardiogram of rats cooled to lethal levels were investigated.

Both the heart rate and the conduction of the cardiac impulse were slowed by reduction of the body temperature. The relationship of the heart rate to the body temperature was linear over the range from 15° to 35° C. (59° to 95° F.), with a Q_{10} of 2.14, and had a high positive correlation. The slowing of conduction in the heart was proprtional to the change in heart rate.

During the reduction of body temperature, the arterial pressure increased as the shivering became maximal down to a rectal temperature of 29° C. (84.2° F.). Further reduction of temperature resulted in a decline of arterial pressure, at first gradual, until the temperature reached about 23° C. (73.4° F.), and then precipitous, as the temperature fell below 21° C. (69.8° F.). The relation between arterial pressure and heart rate became linear after the heart had slowed to about one-third the normal rate. Complete atrioventricular block was observed only after the arterial pressure had reached levels below 80 mm. of mercury.

Abnormalities of the P wave and complete atrioventricular dissociation were the most striking features at low temperatures. The arrhythmias were of two types: sinoatrial block with shift of the pacemaker to other parts of the atria and finally the establishment of atrioventricular nodal rhythm and complete atrioventricular block. The first type was reversible by raising the body temperature slowly; the second may be corrected by administering artificial respiration, or may disappear when the temperature rises slowly during recovery.

Respiratory arrest in hypothermic rats occurred only after the arterial pressure had fallen below 70 mm. of mercury. The circulatory failure preceding respiratory arrest was closely related to the degree of cardiac slowing.

AUTHOR.

Member, S., Bruger, M., and Oppenheim, E.: Experimental Atherosclerosis. Arch. Path. 38: 210, 1944.

Cholic or glycocholic acid fed with cholesterol to the rabbit increases markedly the cholesterol contents of the whole blood and the aorta as compared with the levels obtained following the ingestion of cholesterol alone.

Dehydrocholic acid, hyodesoxycholic acid, and desoxycholic acid do not possess this property.

In two series of experiments in which desoxycholic acid and glycocholic acid were used, respectively, the latter was shown to augment the cholesterol content of the liver; the former was without effect in this regard.

The feeding of cholic acid, unlike that of any other bile acid tested, is accompanied by increased concentration of combined (ester) cholesterol in the whole blood.

AUTHORS.

Sharpey-Schafer, E. P.: Cardiac Output in Severe Anaemia. Clin. Sc. 5: 125, 1944.

This paper reports results obtained in posthemorrhagic and chronic anemia including some cases showing evidence of congenital heart failure for which no cause other than anemia was discovered. The author used a method of cardiac catheterization as a means for determining cardiac output and by the same method was able to measure directly the mean right auricular pressure and percentage of utilization of available oxygen.

Resting minute oxygen consumption was not reduced in chronic and posthemorrhagic anemia. Oxygen supply was maintained by increased cardiac output which at the lowest hemoglobin levels approximated the minimum necessary output, increased removal of oxygen in the periphery (up to 90 per cent of available oxygen), and reduced blood volume, resulting in greater concentration of total hemoglobin.

Venous pressure is increased in the most severe cases. This congestive heart failure in anemia was associated with increased cardiac output and decreased blood volume. Passive venous congestion will not explain these findings and conspicuous increase of venous pressure may represent the last stage of a process of adjustment, which maintains the necessary minute output.

The phase of increased cardiac output and pulse pressure after hemorrhage did not develop immediately and was preceded in three cases by a phase of low blood pressure and probably reduced cardiac output.

AUTHOR.

Berconsky, I.: Preventive Treatment of Supraventricular Paroxysmal Tachycardia With Carbamilcolina. Rev. argent. de cardiol. **11:** 120, 1944.

Carbaminoylcholine chloride (Carbachol), in doses of 4 mg. per day, was used as a preventive of attacks of supraventricular paroxysmal tachycardia. In four patients with frequent crisis, this treatment prevented the attacks where quinidine and digitalis had previously failed.

AUTHOR.

Dubin, I. N., and Hollinshead, W. H.: Congenitally Insufficient Tricuspid Valve Accompanied by an Anomalous Septum in the Right Atrium. Arch. Path. **38:** 225, 1944.

In the case described the tricuspid insufficiency apparently resulted from lack of differentiation of the tricuspid valve, hypoplasia of the papillary muscles and aplasia of most of the chordae tendineae. The heart contained a large anomalous septum in the right atrium, probably representing a persistent right valve of the sinus venosus.

AUTHORS.

Shapire, M. J.: Preoperative Diagnosis of Patent Ductus Arteriosus. J. A. M. A. **126:** 934, 1944.

Rickettsial spotted fever is a severe systemic disease. It is rarely diagnosed until the skin rash has appeared. No specific therapeutic agent is available which is effective after the third day of the rash; hence, therapy must be largely supportive.

Regulation of supportive therapy, based on the pathologic physiology of the disease, has not been attempted. Because of the vascular lesions, the loss of circulating body fluids, particularly protein, is analogous to that in burns, and peripheral circulatory collapse may develop if inadequate or improper treatment is given. The administration of saline solution or glucose without blood or plasma will aggravate, rather than correct, the abnormal physiology by washing out further protein.

Intravenous therapy, properly chosen, is not harmful, as it has been reported to be, but may prove lifesaving. It should include plasma and whole blood in adequate quantities in addition to glucose, salts, vitamins, and amino acids. Careful laboratory control in choosing the type and quantity of parenteral or oral fluids to be administered is important.

The elevation of the blood nonprotein nitrogen and lowering of blood chlorides are connectable.

Edema of the subcutaneous tissues and lungs can be produced by excessive administration of crystalloids. The increase in water binding power of the circulating fluid, produced by the administration of blood and plasma, pulls water out of the interstitial spaces and reduces the edema. The peripheral circulation can be supported and the blood pressure raised from shock levels.

The serum proteins are produced; nitrogen excretion studies suggest that protein destruction is great. The impairment of liver function makes protein replacement therapy necessary for variable lengths of time.

AUTHOR.

Coulter, W. W., and Marcuse, P.: Acute Isolated Myocarditis. Am. J. Clin. Path. **14**: 399, 1944.

A case is reported in which a nonspecific type of myocarditis and less marked nonspecific changes in the lungs and liver were the pathologic findings. The lesions in the heart muscles were severe enough to account for the patient's sudden death after a short illness with vague symptoms.

AUTHORS.

Waitzkin, L.: Impending Myocardial Infarction. Ann. Int. Med. **21**: 421, 1944.

Acute myocardial infarction is preceded by premonitory symptoms in a goodly percentage of cases. In a patient previously well, cardiac pain, however brief and mild, suddenly appearing during rest or customary activity, may imply existing or imminent myocardial infarction. In a case of pre-existing angina pectoris, cardiac pain, more readily precipitated by effort or beginning to occur at rest, may imply existing or imminent myocardial infarction. In considering symptoms suspected as premonitory it must be recognized that myocardial infarction does not inevitably follow them, but the strong possibility that it may should lead to heightened suspicion and therapeutic precautions.

AUTHOR.

Pease, P. P., Steuer, L. G., and Peters, C. H.: Value of the Electrocardiogram in Acute Rheumatic Fever. Mil. Surgeon **95**: 287, 1944.

The value of routine serial electrocardiograms in acute rheumatic fever has again been pointed out. Three cases are reported showing electrocardiographic evidence of cardiac damage which might have otherwise escaped detection.

AUTHORS.

Taran, L. M., Jablon, J. M., and Weyr, H. N.: Immunologic Studies in Rheumatic Fever. I. Cutaneous Response to Type-Specific Proteins of the Hemolytic Streptococcus. A. Response to Combinations of "M" Proteins From Selected Types of Hemolytic Streptococci. J. Immunol. **49**: 209, 1944.

Cutaneous reaction to the M fraction of twenty-five known Griffith types of hemolytic streptococcus was studied in rheumatic children, their normal siblings, and normal children. The incidence of positive cutaneous reaction in normal children is 65 per cent as compared with 83 per cent in rheumatic children. The

incidence of positive cutaneous reaction in the normal siblings of these rheumatic children is the same as in rheumatic children.

The cutaneous reactions of normal children are of a significantly milder degree than those of rheumatic children and their siblings; the highest degree of reactivity was found in the normal siblings of rheumatic children.

The incidence and the degree of cutaneous reaction to the M fraction of the hemolytic streptococcus are not influenced by the age of the child, between the ages of 6 and 16 years, or by the rheumatic status; active cases do not show a higher incidence or degree of cutaneous reactivity.

Cutaneous reactivity to specific M fraction in rheumatic children diminishes only slightly with the lapse of time following an acute rheumatic episode.

AUTHORS.

Mendelson, C. L.: Management of Delivery in Pregnancy Complicated by Serious Rheumatic Heart Disease. Am. J. Obst. & Gynec. 48: 329, 1944.

The successful management of pregnancy complicated by serious rheumatic heart disease requires a program of medical and surgical obstetrics of the highest order. Barring other obstetric complications, the vast majority of cases can be successfully delivered by the vaginal route. When indicated, vaginal therapeutic abortion is a relatively safe procedure for interruption of early pregnancy.

The hazards of labor can be definitely reduced with good ante-partum care, careful functional evaluation, adequate digitalization, and shortening of the second stage. The pulse and respiratory rates intrapartum provide a valuable guide to the cardiac status. Abdominal delivery has been performed with decreasing frequency, and yet it may still have its place in those patients who fail to improve in spite of treatment. Each patient should be evaluated as an individual problem. Once severe cardiac failure has occurred ante partum, there is a great risk in discharging the patient from the hospital before delivery.

The incidence of spontaneous abortion and premature labor, the duration of labor, and the blood loss at parturition in women with serious rheumatic heart disease are not significantly different from values in normal women.

AUTHOR.

Salit, E. P., and Tuttle, W. W.: The Variability of Heart Rate and Blood Pressure in Selected Groups of College and High School Students. J. Lab. & Clin. Med. 29: 1139, 1944.

Pulse after a standard exercise is a more reliable measure than the resting pulse, but the resting systolic blood pressure is a more reliable measure than the systolic pressure after exercise.

Even when conditions are carefully controlled, an individual's heart rate and blood pressure are so variable from day to day that a number of determinations must be made if his general status is to be established.

Cardiovascular tests in general have little discriminatory power because the differences in scores among individuals are small in relation to individual variability.

Individuals can more clearly be distinguished from each other on the basis of postexercise pulse rates than on the basis of resting heart rate or the increase due to moderate exercise. The same is true of postexercise systolic and diastolic blood pressures.

The relative efficiency of heart rate scores in distinguishing individuals from each other has been demonstrated in terms of the percentage of significant differences among individuals in a group. Whereas only 8 per cent of the differences in the resting pulse for the twenty men in our experiment are significant at the 1 per cent level of confidence, 41 per cent of the differences in pulse one-half minute after exercise are significant at this level. The corresponding figures for the women

are 25 per cent and 32 per cent. At the 5 per cent level of confidence, 62 per cent of the differences in pulse after exercise are significant among the men; among the women only 53 per cent of the differences are significant at this level of confidence.

AUTHORS.

Webb, A. C.: Periarteritis Nodosa in Pregnancy. Arch. Path. 38: 329, 1944.

Periarteritis nodosa was observed in a parturient woman whose death most probably can be ascribed to severe toxemia and puerperal sepsis. The role played by the lesions of periarteritis nodosa in relation to the death of the patient cannot be evaluated.

AUTHOR.

Hines, E. A., Jr.: The Prevention of Venous Thrombosis and Pulmonary Embolism. J. South Carolina M. A. 40: 159, 1944.

Some of the general measures which may be of help in the prevention of postoperative venous thrombosis and pulmonary embolism are: careful surgical technique with avoidance of trauma to tissue and especially to blood vessels; the preoperative and postoperative treatment of anemia; avoidance of abdominal compression by tight compresses and bandages; adequate fluid intake; prompt treatment of infection; warm environmental temperatures, especially about the lower extremities; respiratory and leg exercises and massage; and keeping the patient in bed for as short a period as practicable.

The author also discusses the special methods used for the prevention of anticoagulant therapy and ligation and division of the femoral and iliac veins and thrombectomy. It is his opinion that the operative procedure is less safe and more conducive to permanent chronic venous insufficiency than is adequate and properly controlled anticoagulant therapy.

AUTHOR.

Chess, S., Chess, D., and Cole, W. H.: Experimental Tourniquet Shock With Particular Reference to the Toxic Factor. A Method of Production Eliminating the Influence of General Anesthesia and Nervous Impulses. Arch. Surg. 49: 147, 1944.

Tourniquet shock can be produced consistently in animals and is therefore particularly adaptable for study, but the extreme pain produced by the tourniquet makes it necessary to utilize some type of anesthesia. Prolonged anesthesia, whether produced by a barbital compound or a general anesthetic, is undesirable. Moreover, since nervous impulses are obviously so intensive, this factor might alter the data derived from the experiment. To obviate these disadvantages we have adopted the procedure of cutting the spinal cord at the level of the lowest dorsal or the uppermost lumbar vertebra, two to four days before the experiment is to be performed. It is unwise to wait much longer, since the anesthesia induced in the lower extremities, which are dragged over the floor of the cage, may allow development of ulcers, infection, etc. Manipulation or operation may be conducted without pain on the lower extremities of the animal with no more anesthetic than a moderate dose of morphine. To keep the tourniquet anchored in one place a sterile nail can be driven deeply into the trochanter. In the experiments in which shock was produced by release of the tourniquet, death always occurred if the tourniquet had been left in place for at least nine hours. In ten animals studied by this method, death occurred after an average of two hours and thirty-four minutes following release of the tourniquet. The average loss of plasma into the extremity before and following release of the tourniquet, as determined by the method of Blalock, was only 2.1 per cent of the total body weight, which is insufficient in itself to explain death.

To determine whether or not a toxin may have developed in the constricted limb and may have been an important factor in the pathogenesis of shock and death, we performed cross transfusion, injecting blood obtained from the distal portion of the femoral vein of the constricted limb into a normal (control) animal. To prevent increase in shock in the animal subjected to the application of the tourniquet through loss of blood, an equal amount of blood was removed from the recipient (control) animal, and injected into the shocked animal.

Because of exigencies of war, work on the problem was interrupted; only five such experiments could be performed. Four of the five animals receiving blood from the constricted limb after release of the tourniquet died two to twelve hours after the transfusion was begun. The only dog to survive transfusion of blood which had circulated through the contricted limb was one which did not receive any blood from the constricted limb until ten minutes following release of the tourniquet. If a toxin were present in the constricted limb it would supposedly be more concentrated in the blood draining from the limb during the first few minutes following release of the tourniquet. If this were true, survival of this animal, which, however, did go into shock during the transfusion (but recovered afterward), might be explained.

AUTHORS.

Joselevich, M., and Mactas, B. A.: Radiologic Image of the Arch of the Azygos Vein in Cardiovascular Disease. Rev. argent. de cardiol. **11**: 98, 1944.

Out of 1,287 chest x-ray films of ambulatory patients, one hundred ninety per cent (15 per cent) showed the right paratracheal image corresponding to the normal course of the arch of the azygos vein and seven (5.4 per cent) showed the presence of the Wrisberg's lobe.

The x-ray films were classified in six groups according to the clinical diagnosis of the patients: various noncardiac; pulmonary; rheumatic fever; heart disease, compensated; arterial disease, compensated; cardiac insufficiency.

The paratracheal images were classified according to size in two types: with longitudinal and transverse diameters of less than 15 and 5 mm., respectively, and with diameters greater than these. Images of both were found in a proportion of 83.9 and 16.1 per cent, respectively, in patients of the first mentioned group; of 65 and 35 per cent in those of the second group; of 66.6 and 33.3 per cent in patients of the fourth group; of 58.1 and 41.8 per cent in those of the fifth group; and of 30 and 70 per cent, respectively, in patients of the last group.

Of the fourteen images of the second size found in the group of noncardiac patients, seven corresponded to pregnant women and three to hyperthyroids. Of twelve patients with cirrhosis, five showed the paratracheal image: three of the first size and two of the second size.

Our results tend to confirm the findings of others which showed an increase in size of the paratracheal image in cardiac insufficiency, in hyperthyroidism (in both cases due probably to a high venous pressure), and in cirrhosis of the veins. The same finding was made in the seven cases of Wrisberg's lobe, showing that the arch of the anomalous azygos vein responds as the normal to the causes which determine the increase of its radiological shadow.

AUTHORS.

Sherman, C. F., and Ducey, E. F.: Cardiac Mensuration. Am. J. Roentgenol. **51**: 439, 1944.

A direct comparison was made between the transverse cardiac diameter of two hundred adult males, obtained within ninety days of death, and the weight of their hearts at autopsy.

In this study, the results by the Ungerleider method are much more closely correlated with the actual cardiac weight than are those of the other two roentgen methods studied.

There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight as calculated from Zeek's table. This correlation expressed numerically has a value of 1:3.3.

Marked deviation from normal body weight and pericardial effusion greater than 200 c.c. impair the accuracy of the method to such an extent as to preclude its use without qualification.

AUTHORS.

Monahan, D. T.: Ligation of the Aorta and Both Common Iliacs for Aneurysm. Surgery 16: 519, 1944.

A case is reported in which the aorta was occluded in stages by rubber bands proximal to an aneurysm with division of both common iliac arteries. The patient lived approximately five months from the time of the first ligation. Seven cases of aortic ligation are reviewed. Of these, there were four partial, and three total, occlusions. Of the three total occlusions, two patients had collateral established at the time of operation, and the third had alarming paralysis of the extremities following ligation, and survived probably because of his youth.

Occlusion of the lower abdominal aorta is feasible. Furthermore, man will tolerate division of both common iliacs after ligation of the aorta. Cotton tape has been demonstrated as the least noxious material for ligation. It seems reasonable that ligation in stages with cotton tape, plus ligation of both iliacs, should cure aneurysms of the lower abdominal aorta.

AUTHOR.

Lazarus, J. A., and Marks, M. S.: Aneurysm of the Renal Artery—True and False—With Special Reference to Preoperative Diagnosis. J. Urol. 52: 199, 1944.

Aneurysm of the renal artery is a rare clinical entity, as evidenced by the fact that we were able to collect only seventy-five cases from the literature. This includes the case here presented.

A history of trauma was elicited in 34.7 per cent of these cases. Among the other etiological factors associated with this condition are systemic debilitating infections and atherosclerosis.

Pathologically, aneurysms may be classified as (a) true and (b) false. True aneurysm is a saccular dilatation of an artery containing all the elements of the arterial wall and results from weakening of the arterial wall as a result of sclerosis, fatty degeneration involving the elastic fibers from some debilitating systemic infection, or atherosclerosis. A false aneurysm is a saccular dilatation of an artery due to trauma resulting in complete disruption of continuity of the arterial wall either in part or in its entirety, in which the limiting walls from without inward consist of adventitia, laminated blood clot, and endothelium.

Small aneurysms of the renal artery usually give rise to no symptoms. Larger aneurysms, however, usually give rise to symptoms, the most common of which is pain in the loin (62.7 per cent). A mass was felt in the loin in 30 per cent of the recorded cases.

The presence of an opaque ring shadow with dense periphery on the x-ray film in the region of the renal pelvis is an extremely valuable diagnostic sign of this disease.

The indicated procedure in the treatment of renal artery aneurysm is immediate nephrectomy with ligation of the renal artery proximal to the point of origin of the aneurysm.

A case is reported of aneurysm of the renal artery associated with calculus pyonephrosis, in which a correct preoperative diagnosis was made by finding a typical ring shadow on the x-ray film in the region of the renal pelvis. Owing to the location of the aneurysm, the lesion was missed at operation, but was clearly disclosed on pathologic examination of the extirpated kidney.

AUTHORS.

Yonkman, F. F.: Toxicity of Yohimbine Hydrochloride. J. Lab. & Clin. Med. **29**: 1222, 1944.

Yohimbine, fed ad libitum to rats in drinking water, seems to be nontoxic for over three months except when the concentration in the water is increased to 1:1,000. On higher dilutions, growth and vigor are generally maintained at good levels and habits are normal. Autopsy findings are essentially normal.

AUTHOR.

Quick, A. J.: Anitcoagulants Effective in Vivo With Special Reference to Heparin and Dicumarol. Physiol. Rev. **24**: 297, 1944.

The normal antithrombin of the blood is closely associated with the albumin fraction. It does not inhibit or retard coagulation, but merely inactivates thrombin. Quantitative methods have been developed for its determination, but the significance of its variation in the blood remains obscure.

Heparin, the natural physiologic anticoagulant, is a compound closely related to mucoitin-polysulfuric acid. Due to its strongly acidic character, it forms complexes with various proteins and other biologic compounds. Heparin per se is not an antithrombin, but with a cofactor present in serum albumin forms a strong thrombin-inactivating complex. Heparin in inhibiting the conversion of prothrombin to thrombin likewise requires a cofactor which is present in the plasma. Heparin prevents the agglutination of platelets, probably by virtue of its anticoagulant action. The function of heparin in the body has not been determined. It is liberated during anaphylactic and peptone shock, but the mechanism whereby this is brought about is still obscure, and the purpose of this physiologic response has not been ascertained.

Antithromboplastin has been demonstrated in the blood, and evidence has been found that it is abnormally increased in hemophilic blood.

Dicumarol is the toxic principle isolated from spoiled sweet clover hay. It is a coumarin derivative which had not hitherto been known to occur in plants. When dicumarol is administered orally or intravenously to man or animals, it causes a gradual but severe decrease of the prothrombin of the blood (or more accurately of component B of prothrombin). Several days are required for the production of its full effect, and recovery is equally slow. Evidence is accumulating which suggests that vitamin K has some antagonistic action against dicumarol. The hypoprothrombinemia produced by the drug can be temporarily alleviated by transfusion. Dicumarol appears to have no toxic action other than depressing the prothrombin except in excessive dosage. It is probable that some of the pathologic findings in fatal cases of dicumarol poisoning can be attributed to tissue anoxia due to the severe anemia after excessive hemorrhage.

Salicylates especially when given to animals on a low vitamin K diet depress the prothrombin of the blood but to a much smaller degree than dicumarol. Sulfaguanidine and succinylsulfathiazol also cause a hypoprothrombinemia, but the action appears to be due to a depression of the synthesis of vitamin K by the bacteria of the intestines and not to a direct action on the synthesis of prothrombin.

AUTHOR.

Book Reviews

CLINICAL HEART DISEASE: By Samuel A. Levine, M.D., Assistant Professor of Medicine, Harvard Medical School. Ed. 3, W. B. Saunders Company, Philadelphia, 1945, 462 pages, 157 illustrations, $6.00.

The author states that the general character of the book has not been changed from that of previous editions. The discussion of the surgical treatment of patent ductus arteriosus and of the chemotherapy of subacute bacterial endocarditis has been amplified, the latter to include penicillin. Brief reviews of scleroderma heart, rupture of valves, and the heart in Addison's disease have been added. The discussion of electrocardiography has been elaborated. A few phonocardiograms are reproduced in this edition.

The book is intended for the general practitioner. Its popularity is attested by the frequency with which new editions appear. The subject matter is presented in clear and simple form and, in general, reflects the most widely accepted views. The author seems to be at his best when he discusses treatment, although the part of the presentation of electrocardiography dealing with abnormal cardiac mechanisms is also very well done. He belongs to the school of thought which holds that, as a rule, only one chest lead, in addition to limb leads, is necessary for the study of myocardial damage, although he does concede that, in case of doubt, three or six chest leads may be useful. Like most authors of books on the heart, he does not appear to be troubled by doubt as to the complete validity of the Einthoven equilateral triangle hypothesis and all the tidy concepts erected upon it.

CHARLES C. WOLFERTH.

Erratum

In the article entitled "The Effect on the Blood Pressure of Normal Persons and Hypertensive Patients of Glyceryl Trinitrate, Sodium Nitrite, Erythrol Tetranitrate, and Mannitol Hexanitrate," by John C. Weaver, J. H. Wills, and H. C. Hodge, which appeared in the November, 1944, issue of the JOURNAL, volume 28, page 603, the dose of nitroglycerin, given in the second line of the first paragraph, should read 0.0006 Gm. instead of 0.006 Gm.

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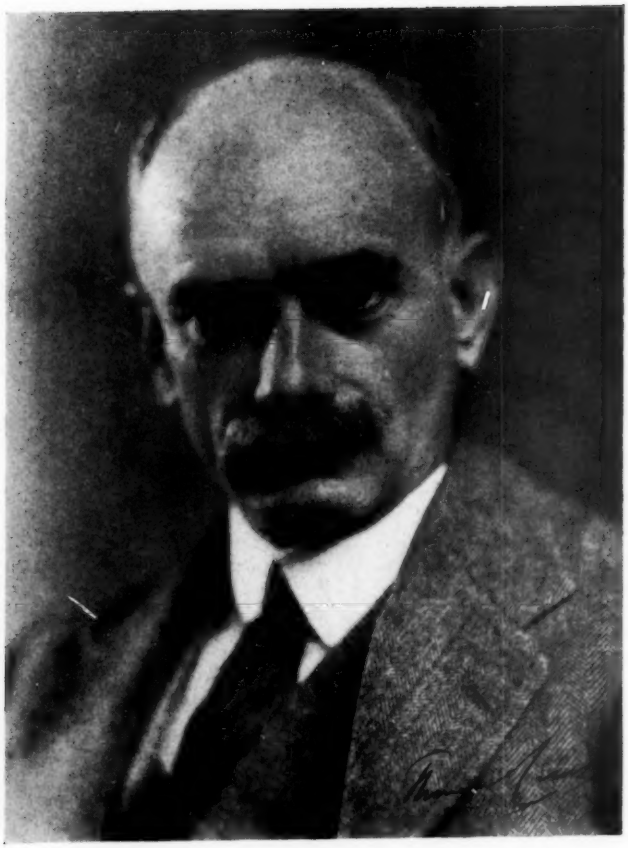

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